PATHOGENESIS AND TREATMENT OF ENDOCRINE EXOPHTHALMOS *

Sir RUSSELL BRAIN
Bt., D.M. Oxon., D.C.L., LL.D., F.R.C.P.
PHYSICIAN TO THE LONDON HOSPITAL AND THE MAIDA VALE HOSPITAL

IT is just twenty years since I coined the term "exophthalmic ophthalmoplegia" (Brain 1938). During that time much work has been done on the experimental production of exophthalmos, and yet we are still ignorant of its fundamental nature. Hence our treatment of endocrine exophthalmos is still empirical. When I wrote my paper I had seen 31 cases of exophthalmic ophthalmoplegia in seven years. Now I have seen over 200.

Having discussed the history of exophthalmic ophthalmoplegia in my 1938 paper, I shall not say more about it now than to recall that the first case I was able to find on record was that of Naumann (1853), while another case, reported by Warner (1883), was that of a woman who was admitted to the London Hospital with Graves' disease, exophthalmic ophthalmoplegia, and weakness of the muscles of mastication and those of the face and limbs. This patient improved considerably, but died three years later. An increase in the orbital fat, and stretching and pallor of the ocular muscles, were observed at necropsy by Bristowe (1886). Thus all the cardinal features of the syndrome had been observed more than 70 years ago. In 1938, I said:

"The association of ophthalmoplegia with exophthalmos and general symptoms of thyrotoxicosis has been known for over 80 years. Hitherto the ophthalmoplegia has been regarded either as an unusual complication of exophthalmic goitre, or as evidence of the association of myasthenia gravis with this disease. Certain clinical features, however... taken in conjunction with the recent increase in our knowledge of the physiology of the thyroid gland, have convinced me that neither of these views is correct and that exophthalmic opthalmoplegia is a syndrome distinct from both exophthalmic goitre and myasthenia gravis. Briefly, these distinguishing features are that exophthalmic ophthalmoplegia differs from exophthalmic goitre in both age and sex incidence and, a point of cardinal importance, in the role of the thyroid in its aetiology. Whereas in Graves' disease thyrotoxicosis is an essential, and indeed the principal, disorder of function, in exophthalmic ophthalmoplegia thyrotoxicosis plays no essential part".

But "there is an exception to every statement that can be made about exophthalmic ophthalmoplegia" (Brain 1952). This is another way of saying that our ideas of the nature of the disorder have hitherto been inadequate because they have failed to take into account unknown factors, which then make themselves felt by producing the exceptions to any generalisation. In other words again, our explanations have been too simple.

The experimental work of the last twenty years has contributed so far very little to our understanding of the pathogenesis of exophthalmos in man. Nevertheless we can learn from the experimentalists the complexity of the problem and the multiplicity of the factors involved. So far neither clinical observation nor human pathology has been any more successful than experimental physiology. I do not think that the problem of the nature of endocrine exophthalmos in man can be solved either by experimental physiology or by clinical observation and human pathology alone. Experimental physiology is too simple, and our clinical experience contains too many unknowns. Somehow we have to bridge the gap, and this I believe may best be done by looking in either field for facts which may help our understanding of the other. I shall begin by reviewing some of the experimental observations, partly because they are simpler than clinical observations, and partly because they are expressed in terms of normal or disordered physiology—i.e., in those concepts to which we are seeking to reduce our clinical observations. It is essential that we should approach both spheres of investigation with an open mind, and be prepared to question, if necessary, even those ideas which we have taken for granted.

The Experimental Production of Exophthalmos

The older clinicians, observing in exophthalmic goitre the association of exophthalmos and thyrotoxicosis, not unnaturally assumed that the exophthalmos was produced by the thyrotoxicosis, and exercised much ingenuity in trying to find some orbital mechanism by which this could take place, usually invoking the cervical sympathetic. It is often useful to try to discover the ideas one is taking for granted, and two ideas which this older view did take for granted have continued to influence our thinking on the subject until today. The first is that the production of exophthalmos probably has a comparatively simple explanation, such as an excess of thyroxine, and the second is that the explanation is to be sought in terms of a disorder which is merely an excess of a normal function—too much of a good thing, so to speak. So the older and more imaginative endocrinologists were inclined to look for the cause of protrusion of the eye in the excessive activity of some physiological mechanism brought into action by fright or fear.

The idea that an excess of thyroxine was responsible for exophthalmos came to be questioned on three principal grounds:

1. Experimental physiologists claimed that the administration of thyroid extract or thyroxine very seldom produced exophthalmos, and clinical observation suggested that the same was true of man (Brain 1936).

2. Confirmation of this view seemed to come from experimental work (which I shall shortly describe in more detail) which showed that endocrine exophthalmos could readily be produced by injections of extracts of the anterior lobe of the pituitary, and more readily in animals from which the thyroid had been removed than in an intact animal.

3. In exophthalmic ophthalmoplegia there appeared to be no correlation between the presence and degree of the exophthalmos and the state of thyroid activity, and many of the worst instances of progressive exophthalmos occurred in patients who were subthyroidal.

A recent paper by Langford (1957) provides one of those exceptions to which I have drawn attention.

Working with the minnow, *Fundulus heteroclitus*, he produced exophthalmos with triiodothyronine and desiccated thyroid, but not with a pituitary preparation. He offers some criticism of previous work in which it was claimed that thyroid or thyroxine failed to produce exophthalmos in the guineapig, and draws from his own work the conclusion that "the experimental production of exophthalmos should be evaluated critically and that the exclusive role of the pituitary should be subject to especially searching scrutiny". We must obviously be cautious in applying to man observations made

*The Savill oration delivered at the West End Hospital for Nervous Diseases on Oct. 16, 1958.

on the minnow, but at least we can act on Langford's concluding suggestion.

It is now over twenty years since the early workers, Marine and his collaborators (Marine, Spence, and Cipra 1931–32, Marine, Rosen, and Cipra 1932–33, Marine and Rosen 1934), Friedgood (1934), and Smelser (1937), succeeded in producing exophthalmos in animals by the administration of pituitary extracts. The discovery of the thyroid-stimulating hormone of the pituitary, T.S.H., or thyrotrophin, together with the fact that the commonest endocrine abnormality associated with exophthalmos in man is thyrotoxicosis, suggested that the exophthalmos resulting from the injection of anterior-pituitary extracts might be attributed to this hormone. The following further observations both throw light on the mode of production of exophthalmos and illustrate its complexity:

Dobyns et al. (1953), working with the minnow, claim to have shown that the exophthalmos-producing substance of the anterior pituitary is distinct from thyrotrophin.

Smelser and Ozanics (1954) found that in thyroidectomised guineapigs gonadotrophin, corticotrophin, prolactin, and growth hormone, when injected alone, did not cause exophthalmos; nor was the exophthalmos proportional to the amount of thyrotrophin. But combinations of these pituitary hormones may do so.

Smelser and Ozanics (1955) concluded that corticotrophin augments the exophthalmos due to other anterior-pituitary hormones, but neither corticotrophin nor cortisone alone will produce it. The exophthalmos is not due to the interaction of cortisone with growth hormone, prolactin, or gonadotrophin. They were able to produce exophthalmos with a combination of cortisone and thyrotrophin, either pure or as crude pituitary extract; but combined pituitary hormones, with only traces of thyrotrophin, were more effective than thyrotrophin itself. They therefore postulate some extra factor, so far unknown.

Aterman (1954) suggests that exophthalmos is due to a synergy between thyrotrophin and adrenocortical steroids in excess.

Whatever the precise hormone or combination of hormones concerned, there seems no doubt that the exophthalmos is the result of changes in the whole of the orbital contents. Smelser and Ozanics (1955) say that the increase in the orbital fat is from imbibition of water. The muscle enlargement is due partly to the same cause and partly to work hypertrophy. Smelser (1939), investigating the effects of the injection of pituitary extract into thyroidectomised guineapigs, found that it produced on the average a 35% increase in the weight of the retrobulbar tissues, all of which were involved except the ventral lacrimal gland. The orbital fat, in particular, weighed nearly twice as much as that of controls. To ascertain whether this swelling was confined to the orbital fat, Smelser examined the rest of the fat in the body and found that it reacted differently in different situations. There was only slight swelling of the axillary fat and renal fat. The cervical fat was œdematous in 11 out of 18 animals, and there was considerable swelling of the ovarian fat. Dobyns (1946) confirmed and extended these findings:

He observed a general systemic alteration in the fat depots, the fat being replaced by more translucent gelatinous material. Histologically the fat exhibited oedema and was infiltrated with polymorphonuclear cells and tissue macrophages, which were loaded with fat, and were seen to be turning into fibroblasts. These changes occurred in the fat in the liver and kidneys, and there were also changes in the skeletal and cardiac muscles. These alterations took place whether the thyroid was present or not.

To discover whether the reaction of the orbital fat was in any way related to its situation, Smelser and Ozanics (1949), before administering the hormones, transplanted into the orbit fat from parts of the body where it normally showed little or no reaction to pituitary extract. In such animals the original orbital fat exhibited œdema, but not the transplanted fat. From this the investigators concluded that the swelling of the orbital fat is not a mechanical result of other orbital changes, but is due to a selective response of the orbital fat itself.

There is one other experimental observation which may have some clinical significance. Smelser and Ozanics (1955) observed that thyroidectomy alone produced slight œdema and increase in orbital fat sufficient to cause a slight increase in the protrusion of the eyes.

Evidence Concerning the Part Played by Thyrotrophin in Man

If thyrotrophin plays a part in the production, in man, of exophthalmos or thyrotoxicosis or both, some biochemical evidence of this should be obtainable. Adams and Purves (1957) have recently reviewed this question.

The thyrotrophin content of human plasma, serum, and urine has been assayed by many workers by a variety of methods using a number of different test animals. (Some of the discrepancies in their results are probably due to such differences in their techniques. Moreover when repeated injections have to be used, another possible source of error is introduced—the production of antibodies by the test animal.) It seems to be established that thyrotrophin directly and promptly stimulates release of thyroid hormone from the gland, while excess of thyroxine or triiodothyronine appears to suppress thyrotrophin secretion by the pituitary promptly and completely. Thus normally the production of thyrotrophin and the secretion of thyroxine seem to react on each other, and this view is borne out by the fact that the thyrotrophin level in the blood is usually high in primary myxœdema. Even here, however, the situation may be more complex, as Gilliland and Strudwick (1953) have shown; for a patient with myxœdema, when first examined, may have little or no thyrotrophin in the serum and this may increase or appear after treatment with thyroxine —which suggests that the myxœdema itself may depress the pituitary.

Querido and Lameyer (1955) estimated the serum-thyrotrophin in 18 thyrotoxic patients, 9 with and 9 without serious eye signs. Only 2 of these showed an excess, but Querido and Lameyer point out that even if hyperthyroidism were accompanied by more thyrotrophin than normal in the blood, this could not necessarily be demonstrated.

Gilliland and Strudwick (1956) investigated a group of 17 patients. 9 had thyrotoxicosis with severe eye signs, 5 thyrotoxicosis without severe eye signs, and 3 severe eye signs without thyrotoxicosis. They found that thyrotoxicosis with severe eye signs was associated with a raised thyrotrophin level in the serum, comparable to that of spontaneous myxœdema. Of the 5 patients with thyrotoxicosis without severe eye signs, 3 gave no response and 2 showed a measurable level of thyrotrophin somewhat lower than those with severe eye signs. The 3 patients with severe exophthalmos who were not thyrotoxic showed levels of thyrotrophin which did not differ from normals.

Adams and Purves conclude that the demonstration of an active substance in thyrotrophin assays of blood and urine in hyperthyroidism is of significance, even though it has not been clearly demonstrated that the amount of such thyrotrophin is greater than normal. Their reason

is that, in view of the balanced relation between the production of thyroxine and the production of thyrotrophin, if thyrotoxicosis were due to an autonomous overactivity it would suppress production of thyrotrophin by the pituitary. They infer, therefore, that the presence of thyrotrophin in the blood of thyrotoxic patients indicates that the thyrotoxicosis is itself evoked by the thyrotrophin.

They also point out that if a thyrotoxic patient is rendered hypothyroid, either by drugs or by surgery, the serum-thyrotrophin level rises sharply in the blood. On the other hand, administration of thyroid substance, thyroxine, or triiodothyronine does not suppress thyroid activity in the thyrotoxic patient as it does in the euthyroid person.

Relation Between Human Thyrotrophin and Exophthalmos

Querido and Lameyer conclude that there is no relation between exophthalmos and serum-thyrotrophin level. They point out, however, that this does not necessarily mean that thyrotrophin is unrelated to eye signs. Theoretically a level in the serum may be high both with low or high production. Gilliland (1955) concludes that the high levels of serum-thyrotrophin in most patients with spontaneous myxœdema, in induced myxœdema, and in cretinism—all unassociated with exophthalmos—make it unlikely that thyrotrophin alone is a cause of exophthalmos. Some other factor must be involved. Gilliland thinks that the high levels of thyrotrophin in thyrotoxicosis with severe exophthalmos suggests that exophthalmos is related to pituitary activity; but Gilliland and Strudwick (1956) showed that severe exophthalmos can exist without a raised thyrotrophin level, and on the other hand a raised thyrotrophin level can exist without exophthalmos. Dobyns and Wilson (1954) produced exophthalmos in the minnow by injecting the serum of patients with severe or progressive exophthalmos, and their findings suggested some correlation between the degree of response in the fish and the stage and severity of the patient's exophthalmos. Barraquer and Canadell (1956) have made similar observations.

Adams and Purves say that in assays of sera from exophthalmos cases they have found an abnormal type of response. They conclude that

". . . hyperthyroidism is best explained by the presence of a circulating thyroid stimulator, the secretion of which is not suppressed by excess thyroid hormone . . . In cases showing marked exophthalmos a substance of the same nature appears to be present in greater quantity and is demonstrated by a number of different methods, presumably specific for thyrotrophin. The evidence is strongly suggestive that this material plays a causal role in the production of exophthalmos, since it appears to be more easily demonstrated in the group with the most severe exophthalmos. To explain the exophthalmos, however, it is necessary to assume that the substance demonstrated is an abnormal form of thyrotrophin with properties not possessed by the normal pituitary secretion, or is accompanied by some other material which acts synergistically with it to produce exophthalmos ".

Greene and Farran (1958) have shown that D-thyroxine, while it has little of the metabolic effect of L-thyroxine, appears to be active in suppressing the secretion of thyrotrophin. Two patients suffering from both thyrotoxicosis and exophthalmos who received D-thyroxine had a complete remission of thyrotoxicosis, presumably as a result of a reduction in their output of thyrotrophin, but this had no effect on their exophthalmos.

Relation Between Exophthalmic Ophthalmoplegia and Thyrotoxicosis

I have reviewed my last 50 cases of exophthalmic ophthalmoplegia in order to ascertain the relation between this disorder and thyrotoxicosis. There were 31 patients who had had thyrotoxicosis which had received some form of treatment before the development of progressive exophthalmos associated with ophthalmoplegia: 20 of these had been treated with antithyroid drugs, 12 with surgery, 3 with radioactive isotopes, and 1 with X rays. Of the 12 who had been treated surgically, 2 had had three operations on the thyroid gland, 1 had had two, and the remainder one. The interval between the initial attack of thyrotoxicosis and the development of exophthalmic ophthalmoplegia was extremely variable. In 11 cases it was less than a year, and in 8 it was more than seven years, the remainder falling between these extremes. The longest interval was twenty years, and this was in one of the patients who had had three operations on her thyroid, the first of which had been performed twenty years previously. Another patient had had thyrotoxicosis treated with thiouracil fifteen years previously. But only 13 of the 31 patients previously treated for thyrotoxicosis were found to be thyrotoxic when they came under observation with exophthalmic ophthalmoplegia.

Looking now at the thyroid activity of the 50 patients with exophthalmic ophthalmoplegia, 23 of these were found to be thyrotoxic, 2 of them only slightly; 24 were regarded as euthyroid, and 3 were hypothyroid. Only 9 of the 50 patients neither had been in the past nor were at the time of examination thyrotoxic. Fluctuations in the degree of thyroid activity were a striking feature in many patients with a long history. Either the initial treatment, which succeeded in abolishing the thyrotoxicosis, was followed by a relapse calling in turn for more treatment (sometimes of the same, sometimes of a different kind), or in some cases, the initial treatment rendered the patient subthyroidal. This led to the administration of thyroid extract, which was sometimes followed after an interval by a further attack of thyrotoxicosis calling for further measures to reduce thyroid activity.

Before we consider the significance of these facts it will be helpful to reconsider the evidence as to the relation between thyroxine and exophthalmos in man. Although it is true that the administration of thyroid extract, in doses sufficient to produce the general manifestations of thyrotoxicosis, does not usually lead to exophthalmos in man, exceptions to this rule have long been recognised. The prolonged administration—often the self-administration—of thyroid extract may produce a condition indistinguishable from exophthalmic goitre, self-maintaining after the withdrawal of the thyroid extract, and requiring the usual treatment of exophthalmic goitre (Bruun 1945). One example of this is included in the present series:

A married woman, aged 46, weighed 14 st. 8 lb. She bought some thyroid tablets and took six a day. In addition she was prescribed dexamphetamine. She took this combination for eighteen months, by which time she had lost 2 st. in weight. She stopped taking the tablets, but continued to lose weight, and noticed that her eyes were swelling. Two months later her neck was swelling also. When seen she weighed only 10 st. 10 lb. and showed all the symptoms and signs of exophthalmic goitre, with limitation of the ocular movements, diplopia, and auricular fibrillation.

I have previously (Brain 1936) reported the case of an obese woman given thyroid extract over many years who

noticed increasing prominence of the eyes. She presented a clinical picture of mild thyrotoxicosis with bilateral exophthalmos. She was taken off the thyroid extract, and gradually became euthyroid—a process accompanied by considerable increase in weight and diminution in the exophthalmos.

We shall have later to consider the fact that rapid reduction in the thyrotoxicosis by treatment is often followed by increase of the exophthalmos and sometimes by the precipitation of exophthalmic ophthalmoplegia. Nevertheless, the reverse sometimes occurs, and radical treatment of the thyrotoxicosis is followed rapidly by a striking improvement in the exophthalmos. Great improvement as a sequel to thyroidectomy is exceptional. Nevertheless some patients who have both exophthalmic ophthalmoplegia and thyrotoxicosis show no improvement in their eyes until their thyrotoxicosis has been treated.

The following patient well illustrates the complexity of the relation between the administration of thyroxine and the development of thyrotoxicosis.

A woman of 79 had been attending hospital for twenty-five years for myxœdema. This was treated with thyroid extract, and ten years previously she was admitted to hospital with marked exophthalmos. She also had ophthalmoplegia, but her basal metabolic rate was only 89%. Over the years her exophthalmos subsided, but her ophthalmoplegia remained. In the right eye she had loss of elevation and abduction, with reduction of depression. In the left eye she had loss of elevation with reduction of abduction. She had all the symptoms and signs of myxoedema, together with pretibial myxoedema and clubbing of the fingers. It was found, however, that she could no longer tolerate thyroid extract. Even the smallest dose, continued for three or four weeks, changed her appearance from that of myxoedema to that of thyrotoxicosis, and she developed a tachycardia which persisted for many weeks after the thyroid extract was withdrawn, and lid-retraction.

These facts raise several important questions.

The first is, how does the administration of thyroid extract lead to an established state of thyrotoxicosis with exophthalmos? In a normal person, the administration of thyroid extract might be expected to depress the production of thyrotrophin by the pituitary and the activity of the thyroid. Certainly some of the patients who are given thyroid extract are not normal to start with. Some have myxœdema; others take the thyroid for obesity, which may in itself indicate a state of endocrine imbalance. Nevertheless, the production of persistent thyrotoxicosis in this way remains for the present an unsolved problem.

The next question is the relation between a previous treated thyrotoxicosis and the development of exophthalmos. There is no doubt that abolition of thyrotoxicosis tends to cause progressive increase in the existing exophthalmos and the development of ophthalmoplegia. This event may follow any form of treatment for the thyrotoxicosis, and in the absence of evidence as to the relative frequency with which different methods of treatment are employed it is impossible to say whether one is more likely to produce it than another. These are the patients in whom progressive exophthalmos immediately follows treatment and therefore usually occurs within a few months of the onset of symptoms of thyrotoxicosis. At the other extreme are patients who have had thyrotoxicosis many years previously, and who may or may not be thyrotoxic when they develop progressive exophthalmos. In this group it seems probable that the previous attack of thyrotoxicosis, and perhaps especially fluctuations in the degree of thyroid activity over a long period, predispose in some way to the subsequent development of progressive exophthalmos.

Finally there is the question whether the thyrotoxicosis in itself directly contributes to the production of the exophthalmos. As long as exophthalmos was attributed to the action of a single factor, it seemed clear that that factor could not be thyroxine. Now, however, that we are encouraged to regard exophthalmos as probably the result of the synergic action of a number of factors, it seems worth considering whether one of those factors may not in some cases be thyroxine. This might perhaps act in some quite general way through its effect on metabolism or on the circulation, and so intensify changes in the orbit (primarily produced by other factors) which by itself it would be incapable of causing. If this is so, it would explain the benefit which sometimes follows thyroidectomy. Apart from this, clinical observation suggests that thyroxine is closely concerned in the production of lid-retraction.

Prunty (1958–59) has drawn attention to the synergic action of hormones and the relation of this to end-organ sensitivity.

The Orbital Changes Responsible for Exophthalmos

One of the many puzzles connected with endocrine exophthalmos is that endocrine exophthalmos has been attributed to different biochemical changes in different circumstances.

Rundle and Pochin (1944) investigated the orbital tissues in 17 patients dying of thyrotoxicosis. They found that the exophthalmos was accounted for quantitatively by an increase in the bulk of the retrobulbar tissues. The increase was relatively greatest in the eye muscles, of which the average fat content was doubled. Increase of fat in the orbital fibrofatty tissue, however, was responsible for most of the increase in bulk. These changes were present both in cases with eye signs and in cases without eye signs.

Rundle, Finlay-Jones, and Noad (1953) analysed the ocular muscles of a patient with exophthalmic ophthalmoplegia. They compared the result with controls and with patients suffering from thyrotoxicosis. The fresh weight of the eye muscles in exophthalmic ophthalmoplegia was about four times that of the controls and three times that in the patients with thyrotoxicosis. Both the dry fat-free residue and the water content were increased, in roughly similar proportions. Thus the muscles in exophthalmic ophthalmoplegia were merely extremely large: they were not œdematous, and there was no relative increase in their water content.

The analysis confirmed the previous observation of Rundle and Pochin that there is a relative increase in fat in the eye muscles in thyrotoxicosis. These, although only one-third of the size, contained 50% more fat than the muscles in exophthalmic ophthalmoplegia. In exophthalmos experimentally produced by the injection of anterior-pituitary extracts, the increase in the volume of the orbital tissues is almost entirely due to an increase in the water content of the fat (Smelser 1943). No change occurs in the lipid content of the orbital fat. Enlargement of the extraocular muscles is largely caused by an increase in the water component. Histologically the changes in experimentally produced exophthalmos and in human exophthalmic ophthalmoplegia are remarkably similar. There is an apparent œdema of the extraocular muscles with round-cell infiltration, and in the later stages fibrosis.

These observations only reinforce our sense of the complexity of the problem. It seems clear that biochemically the changes in the orbital contents in exophthalmic goitre and in exophthalmic ophthalmoplegia are different. The characteristic change in the extraocular muscles in

exophthalmic goitre is an increase in the fat content. As we have seen, there is much experimental evidence that injections of anterior-pituitary extracts lead to a profound histological change in the fatty tissues of the body, especially in those of the orbit. It seems possible, therefore, that the orbital changes in exophthalmic ophthalmoplegia may be due to the effects of one or more pituitary hormones, or one or more of these, together with an excess of adrenal corticosteroids, upon orbital contents, including ocular muscles, which already have an abnormally high fat content as the result of thyrotoxicosis. This would account for the supervention of exophthalmic ophthalmoplegia in patients who are, or have been, thyrotoxic. When the patient has never been thyrotoxic the orbital changes may approximate to those produced experimentally by the injection of anterior-pituitary extracts into thyroidectomised animals. To confirm or disprove these speculations we need more analyses of the orbital contents of patients with exophthalmic ophthalmoplegia arising in different clinical circumstances.

But we have not yet finished with this puzzle. What Rundle and Pochin showed is that there is an increase in the orbital fat in patients suffering from thyrotoxicosis who are also described as having Graves' disease. But we should not draw from their observations the conclusion that the increase in the fat content is the result of the thyrotoxicosis, since we have reason to think that Graves' disease is a complex endocrine disturbance in which other factors besides thyrotoxicosis are present. Incidentally it is of considerable interest that Rundle and Pochin also found an increase in the fat content of the skeletal muscles in their cases. Since their patients with thyrotoxicosis were wasted, and yet the fat content of their skeletal muscles corresponded to that of obese normals, they think that this is probably significant. As we have already seen, there is evidence of the influence of anterior-pituitary hormones on the general body fat as well as on skeletal and cardiac muscle. Rundle and Pochin conclude that "it would seem reasonable to accept the view that severe and mild exophthalmos in Graves's disease are similar in nature and that a common process is operating severely in the one case and mildly in the other." But nine years later Rundle, Finlay-Jones, and Noad recognised that matters are more complex:

"If the orbital changes differ in Graves's disease and malignant exophthalmos it is possible that the basic hormonal upset is different in the two conditions; or that the response of the end organ, the orbital tissue, to the same hormone is different, or that there are usually two closely linked present in roughly inverse proportions. The one, predominating in thyrotoxicosis, would be lipotropic with respect to the orbital tissues as well as thyrotrophic, the other would predominate in malignant exophthalmos and act as an abnormal growth hormone on the orbital and perhaps other muscles. The spontaneous ophthalmic types may represent the result of virtual absence of the lipotropic and thyrotrophic factor."

I can find no basis for the use of the terms "thyrotoxic exophthalmos" and "thyrotrophic exophthalmos". There is no conclusive evidence that thyrotoxicosis alone produces exophthalmos, and there is now little evidence that the thyrotrophic hormone, at any rate acting alone, is responsible for it. We should be wise to be content with the term "endocrine exophthalmos" until we know more about it.

Sex and Age

Now let us look for any possible clues to the role of the pituitary in the production of exophthalmos. Sex is clearly important, for in 100 consecutive cases of exophthalmic ophthalmoplegia females were a little more than twice as common as males (68 females to 32 males); but this is much less than the female preponderance in Graves' disease. The age-incidence also varies in an interesting way in relation to sex (see table). Females tend to be affected earlier than males, and whereas in females the maximum incidence is in the fifth decade, in males nearly half the cases occur in the sixth. It is tempting to speculate that this may indicate a relation between the endocrine changes leading to exophthalmos and the climacteric in both sexes. My youngest patient was 13 and my oldest 80.

PERCENTAGE AGE-DISTRIBUTION IN 100 CASES OF EXOPHTHALMIC OPHTHALMOPLEGIA

—	Both sexes	Males	Females
10–19	1	..	1·5
20–29	..	..	..
30–39	12	3	16
40–49	30	16	37
50–59	35	50	28
60–69	16	22	13
70–79	5	6	4·5
80–89	1	3	..

Some Unusual Endocrine Disturbances Associated With Exophthalmos

Still looking for clues, it seems worth while to draw attention to some unusual endocrine disturbances associated with exophthalmos.

Persistent Lactation

A slight degree of gynæcomastia is not uncommon in males with thyrotoxicosis. I have twice seen enlargement of the breast in a male patient with exophthalmic goitre. One man with exophthalmic ophthalmoplegia had an enlarged breast which secreted a clear fluid. In one of my male patients with exophthalmic ophthalmoplegia, who was being treated at the time with stilboestrol, the breasts secreted a little milk. A much more striking case was the following:

A married woman aged 28, six months after the birth of her second child, developed symptoms of thyrotoxicosis. Subtotal thyroidectomy was performed, and sections of the gland were said to show toxic hyperplasia, but in some parts there was a resemblance to Hashimoto's disease. The operation was followed by tetany and myxœdema, which was controlled by the administration of thyroid extract gr. 4 daily. She also developed exophthalmic ophthalmoplegia, which progressed until I saw her two years later. The normal lactation after the birth of the second child in 1946 persisted and occurred daily until 1954. For the first few years milk actually squirted out of the breasts, but it slowly diminished until only a few drops could be expressed. In 1952 the patient became pregnant again, but the lactation continued unabated. The pregnancy was terminated at $2^1/_2$ months. Menstruation has always been perfectly normal. This patient went to live in South Africa, and her case has been reported by Jackson (1956). She appears to have suffered from overproduction of more than one pituitary hormone.

Lipodystrophy

The association of thyrotoxicosis with progressive lipodystrophy is well recognised but puzzling. Treatment of the thyrotoxicosis may lead to disappearance of the lipodystrophy.

Generalised Œdema

A woman aged 56 had had thyrotoxicosis 14 years previously. In 1941, after severe psychological stress, she

developed thyrotoxicosis, exophthalmic ophthalmoplegia, thyrotoxic myopathy, and generalised œdema for which no renal or cardiac cause could be found. This again suggests that the orbital changes are only the local manifestations of a widespread metabolic disturbance. The patient recovered on medical treatment and now, aged 73, is in good health, except for slight diplopia.

Prognosis and Treatment

Prognosis is important not only in itself but also in relation to treatment. Exophthalmic ophthalmoplegia is on the whole a self-limited disease. This raises its own problems. What is it that brings the pathological process to an end in the course of a year or so? We do not know. Our present therapy is empirical, and so far as it is effective it seems to work by reducing the ill effects of the pathological process rather than by removing its cause. Sometimes, therefore, when the pathological process follows an exceptionally malignant course, our palliative measures will prove insufficient. It has been shown in experimental exophthalmos that even after removal of an eye the orbital contents may continue to increase in bulk.

That process is illustrated by the following fortunately exceptional case:

A man of 57 attended Moorfields Hospital in July, 1939, complaining of proptosis of the right eye. He was found to have slight bilateral exophthalmos. Two months later he was worse, and there was then a corneal ulcer on the left eye. A decompressive operation was performed on the left orbit. A portion of the superior rectus muscle was removed for biopsy, and showed characteristic severe lymphocytic infiltration. The condition continued to progress. In February, 1940, he was given thyroid extract gr. 1 twice daily. After this he became much worse. His right orbit was then decompressed, and he had X-ray treatment to the orbital contents. The pain in the orbit was so severe that he had to be given morphine. When I saw him in March, 1940, he had very severe bilateral exophthalmos, with œdema of the conjunctivae, and both eyes were almost immobile. There were no symptoms or signs of thyrotoxicosis.

I take for granted the cooperation of the ophthalmologist in the management of every case, and I need not stress the value of tarsorrhaphy.

Hormone Treatment

Hormonal treatment, which has been tried empirically or upon somewhat uncertain theoretical grounds, has in my experience proved disappointing. I have not found thyroid extract of any value. If the patient is already thyrotoxic there seems no point in adding to his thyrotoxicosis. If he is not thyrotoxic, there are two possible theoretical reasons for giving thyroid extract. The first is that, as has been suggested, the orbital changes may be due to a localised myxoedema. There is no histological or biochemical support for this. Alternatively, thyroid extract may be given in the hope of diminishing the production of the thyrotrophic hormone. We do not, however, know that the thyrotrophic hormone is the cause of the exophthalmos, and, as we have seen, when the balance between the pituitary and the thyroid is disturbed the production of the thyrotrophic hormone is not always suppressed by thyroxine. Thus there appears to be no firm ground for the administration of thyroid extract, and, if I am right in suspecting that thyrotoxicosis as such may sometimes make the exophthalmos worse, it seems to be contraindicated.

Œstrogens and androgens have been tried with the idea that they also may diminish the output of anterior-pituitary hormones. There is no evidence, however, that they affect in this way any but gonadotrophin, and the administration of œstrogen to rats causes enlargement of the pituitary and even the formation of adenomas (Burrows, 1949). The association of the onset of endocrine exophthalmos with the climacteric might be regarded as an indication for their use, but here again we cannot be sure whether we are doing good or harm by adding to their amounts in the blood. In exceptional cases I have thought that stilbœstrol has done good, but I have no firm statistical evidence of this.

The adrenal corticosteroids have their advocates, but a recent trial under the auspices of a Medical Research Council committee (1955) provided no evidence of their value. This perhaps is not surprising in view of the suggestion that in combination with the pituitary hormones used experimentally they may make the exophthalmos worse. I have had no experience of the use of hyaluronidase.

I was myself responsible for the treatment of 41 out of the last 50 patients whom I saw, the other 9 being seen once only. Of these 41, 9 were treated by thyroidectomy, 15 by X-ray irradiation of the orbits or pituitary (usually the orbits), 6 had bilateral orbital decompression, 1 had unilateral orbital decompression, 1 had one orbit decompressed and the other eye (which was already blind) removed, and 1 had had one eye removed before I saw him. 1 patient had both thyroidectomy and bilateral orbital decompression. This series is not a representative sample, since I have on the whole seen the most severe cases.

Thyroidectomy

The treatment of thyrotoxicosis associated with severe endocrine exophthalmos is a very difficult problem. Dobyns (1945) investigated 233 patients who underwent thyroidectomy for exophthalmic or adenomatous goitre and found that the operation was followed by some increase in the prominence of the eyes. In view of the well-known fact that progressive exophthalmos may date from a sudden therapeutic reduction in thyroid activity, there is a natural anxiety lest such a measure should make the exophthalmos worse. This, however, has not been my experience, and I doubt whether physiologically the two circumstances are strictly comparable. When progressive exophthalmos follows thyroidectomy or some other therapeutic measure which reduces thyroid activity, thyrotoxicosis cannot be a factor in the production of the exophthalmos. On the other hand, when thyrotoxicosis is associated with a progressive exophthalmos, it may—for reasons I have already given—be a contributory factor. If so, there is at least a chance that the patient will benefit as much or more from the abolition of the thyrotoxicosis than he or she may lose from increased output of some other exophthalmogenic factor, which in any case is rather a theoretical risk. I have come to believe, therefore, that in such cases it is important to deal with the thyrotoxicosis, and my own preference is for thyroidectomy. Only one of the 9 patients treated by thyroidectomy also required orbital decompression. When it seems likely that both measures will be needed, which should come first must depend upon the patient's condition. It may be possible to do the thyroidectomy first in the hope of avoiding the necessity for the decompression. On the

other hand, the eyes may be so bad that one has to deal with them first and do a thyroidectomy afterwards.

X-ray Irradiation

Irradiation is, I believe, a valuable palliative measure, and irradiation both of the orbits and of the pituitary have led to an improvement more rapid than I should have expected in the ordinary course of the disorder. My patient aged 80 who was also thyrotoxic was irradiated, and, though his eyes gave cause for much anxiety, he improved, and three years later had been stabilised with little diplopia.

Orbital Decompression

My surgical colleagues have used Naffziger's transfrontal approach for this operation, so I have no experience of any other. A curious and unexplained feature of it, to which attention has been drawn before, is that sometimes, when the worse eye is operated on first, the other one improves so much that it does not need operation. The main indications for orbital decompression are danger to the cornea from raised orbital tension, and danger to vision from papilloedema or (less often) primary optic atrophy.

Conclusions

The treatment of endocrine exophthalmos thus presents many difficulties. Nevertheless, on the whole, time is on the patient's side, and I believe that by taking every aspect of the case into consideration it is almost always possible to obtain a reasonably satisfactory result. Complete disappearance of physical signs is rare, but the visual acuity of both eyes should be normal and double vision should not be an inconvenience. (In suitable cases, when the endocrine changes have subsided, this can be much improved by operations on the ocular muscles.)

There will usually be some residual exophthalmos; but, with disappearance of swelling of the eyelids and conjunctivæ, the patient's appearance should be greatly improved and his general health should be restored to normal.

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THE EFFECT ON HUMAN SERUM-LIPIDS OF A DIETARY FAT, HIGHLY UNSATURATED, BUT POOR IN ESSENTIAL FATTY ACIDS

EDWARD H. AHRENS, JR. M.D. — WILLIAM INSULL, JR. M.D.
JULES HIRSCH M.D. — WILHELM STOFFEL M.D.
MALCOLM L. PETERSON M.D. — JOHN W. FARQUHAR M.D.
OF THE ROCKEFELLER INSTITUTE, NEW YORK

THEODORE MILLER
OF MARINE CHEMURGICS, INC., MOREHEAD CITY, NORTH CAROLINA

H. J. THOMASSON
MED. DRS.
OF THE UNILEVER RESEARCH LABORATORIES, VLAARDINGEN, HOLLAND

NUMEROUS studies (Kinsell et al. 1952, Bronte-Stewart et al. 1956, Ahrens et al. 1957, Malmros and Wigand 1957, Keys et al. 1957) have shown that exchanges of dietary fats have striking effects upon the concentration of lipids in the serum. Thus, unsaturated fats, when substituted isocalorically for fats of more saturated types, appear to produce definite decreases in the serum level of cholesterol and phospholipids. On the basis of long-term clinical feeding experiments in this laboratory (Ahrens et al. 1957) we have suggested that the effects observed are consistently related to the net unsaturation of the dietary fat. But it has been postulated by others (Kinsell and Sinclair 1957) that the serum-lipid effects are due to the content of essential fatty acids (E.F.A.) in the dietary fat. No specific fatty-acid requirement has been demonstrated for adult human beings, but it is conceivable that hypercholesterolæmia in man might represent a biochemical expression of E.F.A. deficiency. Although it is important to distinguish clearly whether the serum-lipid effects described above are due to the E.F.A.-content of dietary fats, or simply to net unsaturation, this question cannot be answered by feeding experiments with natural vegetable and animal fats (Ahrens et al. 1958). However, a partial answer might be obtained with marine oils, since these fats are rich in unsaturation but reputedly poor in E.F.A.

In the present study, a practical procedure was developed for preparing a highly unsaturated marine oil (menhaden oil) which patients found acceptable over many weeks. Bioassay showed that this oil had an exceedingly low content of E.F.A., and chemically the contents of linoleic and arachidonic acid were correspondingly low. The oil was given as the sole dietary fat to two patients for 8-week periods, and the serum-lipid responses were compared with those during periods in which the dietary fat was corn (maize) oil, which is rich in E.F.A. but lower in net unsaturation.

Menhaden Body Oil *

Rendering and Storage

Fresh body oil was prepared from 500 lb. of body portions of menhaden (*Brevoortia tyrannus*) caught in December, 1956, off the North Carolina coast of the United States.

These gill feeders are thought to feed heavily on plankton in more northerly waters before beginning their rapid southward migration. The fish were 12–17 in. long and were in spawning condition. Immediately after being brought aboard

* The generous cooperation of Mr. Charles Butler, of the United States Fish and Wildlife Service, Washington, D.C., is gratefully acknowledged.

the fishing vessel, they were decapitated, eviscerated, and washed with sea water. To decrease bacterial and auto-oxidative changes, the bodies were held in crushed ice mixed with a solution containing 1% sodium bisulphite and 1% phosphoric acid. The temperature was kept at 4°C by repeated additions of ice. The processing of the fish was started as soon as the vessel arrived at the wharf, and it was completed within 15 hours of the time the fish were netted. The bodies were placed in trays in a barrel cooker, steamed for 5 minutes, and immediately transferred to a press. The press liquors were centrifuged to concentrate the crude oil, which was then thoroughly agitated with water at 82°C in an atmosphere of carbon dioxide, before recentrifuging. The washed oil was subjected to a vacuum at 60°C, transferred to pint bottles, flushed with carbon dioxide, and immediately capped and frozen. The containers were stored at −15°C until the oil was required on the metabolic ward.

The final product was pale yellow and semisolid at room temperature. Although unmistakably "fishy" in odour and flavour, it was more bland than any other fish oil tested to date. In separate tests this flavour was not noticeably reduced by steam deodorisation or molecular distillation.

Chemical Data

The iodine value of this oil was 179, peroxide value less than 1, and Gardner colour 10. The oil was subjected to chromatography on silicic acid columns (Hirsch and Ahrens 1958). The total non-triglyceride material was less than 0·2%. Free fatty acids (as oleic) formed 0·1%, lipid phosphorus was present only in trace amounts, and the tocopherol content was 3·2 mg. per 100 g.

The fatty-acid composition was defined by gas/liquid chromatography according to James and Martin (1956), utilising retention-volume data described previously (Stoffel et al. 1958b). Because of the extreme complexity of the fatty-acid pattern, with numerous unsaturated components in each chain-length group, it was necessary to chromatograph the mixed methyl esters on two different stationary phases—Apiezon M (James and Martin 1956) and Reoplex 400 (Orr and Callen 1958). The complementary use of Apiezon M and Reoplex 400 for preparative and analytical chromatography

TABLE I—FATTY-ACID COMPOSITION OF DIETARY FATS AND SERUM-ESTER GROUPS DEFINED BY GAS/LIQUID CHROMATOGRAPHY

(Retention-volume data, calculated in relation to that of methyl stearate, are shown for esters resolved on one or both of two stationary phases. Double-bond content of each acid is shown under "shorthand" designation, i.e., 18 : 2 = a C_{18}-acid with two double bonds. Definitive structures of all even numbered acids have been established [Stoffel and Ahrens 1958, and unpublished].)

Fatty acids					Dietary fats		Patient I						Patient II					
							Menhaden oil (week 14)			Corn oil (week 21)			Menhaden oil (week 16)			Corn oil (week 21)		
No.	Familiar name	Shorthand designation	Retention volumes relative to methyl stearate: Apiezon M	Reoplex 400	Menhaden oil	Corn oil	CE	TG	PL	CE	TG	PL	CE	TG	PL	CE	TG	PL
1	Lauric	12 : 0	0·075	0·18	0·1	0·1		0·1										
2		13 : 0	0·112	0·22	0·1			0·3			0·1							
3		13 : br	0·098		tr													
4		13 : br	0·085		tr													
5	Myristic	14 : 0	0·174	0·32	7·2	0·3	2·1	2·9	1·2	0·3	0·8	0·3	1·1	1·3	0·4	0·2	1·0	0·3
6		14 : br	0·155		0·1													
7		14 : 1	0·159	0·36	0·1			0·2										
8		15 : 0	0·270	0·43	0·5		0·8	0·4	0·5	0·2			0·1	0·5	0·2	0·2		
9		15 : br	0·230		0·2			0·2					tr			0·2		
10		15 : br	0·218		0·2													
11	Palmitic	16 : 0	0·419	0·57	17·0	12·7	30·4	22·4	42·1	9·8	16·9	31·4	23·3	23·7	35·0	12·6	19·9	30·7
12	Palmitoleic	16 : 1	0·366	0·64	9·8		8·4	5·5	2·0	1·0	1·6	0·2	5·6	5·2	1·0	1·6	3·2	0·6
13		16 : 2	0·36	0·77	2·0		0·4	1·8	1·3	0·1	0·2	0·1	tr	0·4	0·2		tr	0·1
14		16 : 2	0·33	0·77														
15		16 : 3	0·324	0·88	1·3													
16		16 : 4	0·314		2·0													
17		17 : 0	0·649	0·74	0·4		0·4	0·3	0·8			0·3			1·3			0·5
18		17 : br	0·500		0·3			0·6						0·5	1·6			0·6
19		17 : br	0·554		0·4													
20	Stearic	18 : 0	1·00	1·00	3·1	2·7	4·2	4·5	23·9	1·0	2·1	14·7	1·0	7·3	15·6	1·0	3·1	14·3
21	Oleic	18 : 1	0·860	1·11	14·5	30·7	21·9	22·2	11·9	17·8	33·4	12·5	21·9	27·7	11·0	18·9	38·1	11·9
22	Linoleic	18 : 2	0·790	1·32	2·0	53·5	9·9	8·4	3·0	62·1	37·4	31·3	16·8	13·4	6·3	59·1	29·3	26·1
23		18 : 2	0·760	1·40	0·7						3·8							
24	Linolenic	18 : 3	0·801	1·66	1·3													
25		18 : 4	0·720	1·91	3·2			1·1		0·4	0·4	0·7				0·3		1·2
26		19 : 0	1·54	1·32	tr													
27		19 : br		1·50	0·4													
28		19 : un		1·59	0·4													
29		20 : 0	2·36	1·78	0·1													
30		20 : 1	1·99	1·96	2·1													
31		20 : 2	1·76	2·24	0·6													
32		20 : 2	1·85	2·24	0·6													
33		20 : 3	1·64	2·68	2·0					0·7		1·7				0·1		1·3
34	Arachidonic	20 : 4	1·46	2·90	0·6		3·1	2·6	1·8	3·9	0·8	3·5	4·2	0·6	4·5	2·6		3·7
35		20 : 5	1·46	3·67	12·5		18·9	19·4	7·2	1·7	0·4	0·8	24·3	11·3	12·9	1·9	1·9	2·0
36		20 : un		4·00				2·8									2·1	
37		20 : un		5·01	0·7													
38		20 : un		5·80	0·5													
39		21 : 0	3·65	2·36	tr													
40		20 : un		3·33	1·7													
41		22 : un		6·30	tr													
42		22 : 5	3·30	6·67	2·0				2·5	1·0		0·7	0·2	2·0	1·8			1·8
43		22 : 6	3·02	7·40	8·9			5·1	1·8		1·0	1·8	1·5	6·0	8·1	0·6	0·9	4·7
44		24 : un			tr													
Saturated acids (% of total)					30·6	15·8	37·9	31·0	68·6	11·3	19·7	46·7	25·5	33·3	52·5	14·6	24·4	46·5
Unsaturated acids (% of total)					69·4	84·2	62·5	69·6	31·4	88·8	80·0	53·3	74·5	66·7	47·5	85·4	75·6	53·5
Mean molecular weight of fatty acids					278·5	277·8	276·1	281·3	273·9	279·9	276·6	276·1	280·3	279·7	280·7	277·2	275·3	278·2
Average no. of double bonds per fatty acid molecule					2·14	1·38	1·58	2·08	0·89	1·76	1·29	1·17	2·09	1·66	1·67	1·64	1·26	1·37
Iodine values: Calculated					189	122	139	144	78	157	113	103	186	148	149	145	110	121
Iodine values: Determined					179	126												
Serum-lipid levels (mg. per 100 ml. serum)							176	180	151	228	530	229	370	155	226	391	175	274

Abbreviations: tr = trace (<0·05%); br = branched acid; un = unsaturated acid; CE = cholesterol esters; TG = triglycerides; PL = phospholipids. Weight concentrations of cholesterol esters calculated from ratios of free/total cholesterol, and from mean molecular weights of cholesterol-ester fatty acids. Iodine values calculated from mean molecular weights of fatty acids and from mean number of double bonds per fatty-acid molecule.

has been discussed elsewhere (Stoffel et al. 1958b). In addition, chromatograms were obtained on the mixed esters after complete hydrogenation (to obtain an accurate chain-length analysis), and after complete bromination (to assure precise analysis of the saturated components). The data on saturated and unsaturated acids in the even-numbered series (left side of table I) are presented with considerable assurance; the odd-numbered acids have not yet been positively identified, but are named according to theoretical considerations (James and Martin 1956). The retention-volume data listed in table I may assist other workers in identifying the numerous components present in other biological mixtures.

Table I shows that menhaden oil is composed of at least 44 different acids. In view of the technical difficulties encountered in defining the quantitative relationships of this complex mixture, it is gratifying to note the close agreement between determined and calculated iodine values for menhaden oil shown at the bottom of the table. This close correspondence validates both the identification of the acids and their quantitation.

C_{18}-dienes constituted 2·0% of the total acids. By degradation studies (Stoffel and Ahrens, unpublished data) this material was shown to be linoleic acid (octadeca-9,12-dienoic acid). C_{20}-tetraene was 0·6% of the total acids; characterisation of the degradation products proved that it was arachidonic acid (eicoso-5,8,11,14-tetraenoic acid). The C_{16}-acids comprised the largest single chain-length group (32% of total acids by weight); the palmitic-acid content of 17% is similar to that reported in other marine oils (Lovern 1950) and in other samples of menhaden oil (Smith and Brown 1945). The C_{16}, C_{18}, and C_{20} unsaturated acids have been fully characterised (Stoffel and Ahrens 1958, Stoffel and Ahrens, unpublished data). Although saturated acids constituted 30% of the total acids by weight, acids with 4–6 double bonds totalled 32%. Thus, the mean number of double bonds per molecule of fatty acid was 2·14, and the mean molecular weight 279 (cf. linoleic acid with 2·0 double bonds, and a molecular weight of 280).

Bioassay

The E.F.A.-content of this sample of menhaden oil was assayed in 60 E.F.A.-deficient rats by the method of Thomasson (1953), and was 4 units per g. of oil (pure linoleic acid is assigned a potency of 100 units per g.). In this 4-week assay of growth, two groups of rats were fed the menhaden oil at dosage levels of 2 and 10 ml. (total per rat) during the first 2 weeks of the test; none of the rats showed signs of toxicity.

Metabolic Studies

Methods

The selection of patients, their management on the metabolic ward, the procedures of feeding, and the clinical laboratory methods have been described fully elsewhere (Ahrens et al. 1957). Two patients were studied for 21 and 22 weeks continuously on the metabolic ward. During this time oral feeding of a liquid mixture (Ahrens et al. 1954) was the sole source of calories, and this was given 5 times per day in amounts such that the body-weight remained constant. Mineral and vitamin supplements were given daily (Ahrens et al. 1957). The protein/fat/carbohydrate composition of the liquid mixture was 15/40/45% of the total calories at all times, and in the two experiments corn oil and menhaden oil were the sole dietary fats in three successive feeding periods. The patients became accustomed in 1–2 days to the corn-oil mixture, and in 3–5 days to the menhaden-oil mixture. While both patients found the menhaden oil unpleasant in taste, at no time was there nausea, vomiting, or diarrhœa.

Supplementary vitamin E was not given, in view of the difficulty in producing E-deficiency in human adults (Horwitt et al. 1956). However, since E-deficiency in animals has been precipitated by feeding highly unsaturated oils (Mason 1954), we were constantly alert to the possibility of the development of creatinuria, myopathy, or encephalopathy. No such symptoms of toxicity nor changes in the sense of well-being were observed. Creatinuria did not occur. Both patients showed lower levels of serum-tocopherol † when taking menhaden oil than when taking corn oil, probably because of decreased intake during the fish-oil period.

Changes in Serum-lipid Levels

Patient I, a 30-year-old white male, showed hyperlipæmia and xanthomatosis of tendons and skin, but no manifestations of cardiovascular disease. He required 2800 calories per day (35 calories per kg.) to maintain constant body-weight. The course of the experiment is shown in fig. 1 and table II. As expected from previous experience (Ahrens et al. 1957), substitution of the corn-oil mixture for an ad-libitum diet produced a striking decrease in all serum-lipid levels; a new steady state was reached in about 3 weeks. When menhaden oil replaced corn oil, there was further depression of cholesterol, phospholipid, and triglyceride values. On reinstitution of corn oil these levels rose, but not to their previous height.

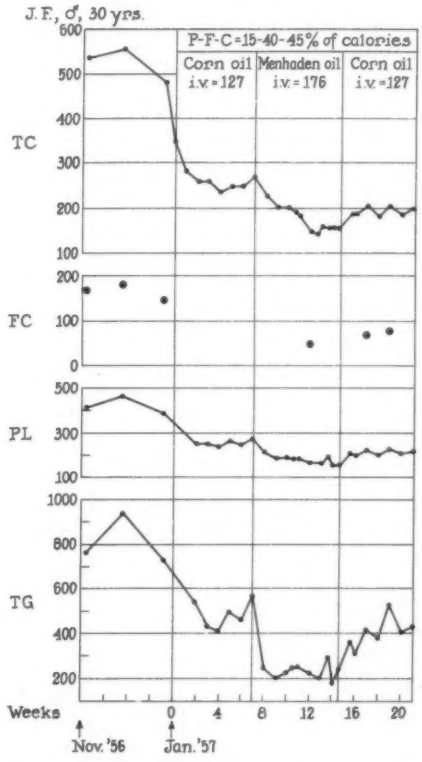

Fig. 1—Serum-lipid changes in patient I when on an ad-libitum diet as an outpatient and when on three dietary regimens in a metabolic ward.

The entire dietary fat intake was composed of corn oil or menhaden oil in successive periods as shown. TC = total cholesterol, FC = free cholesterol, PL = phospholipids, TG = triglycerides, all expressed as mg. per 100 ml. serum; i.v. = iodine value. Each new steady state was preceded by a 2–4 week transition period.

† For these determinations we are deeply indebted to Dr. M. K. Horwitt, of the Elgin State Hospital, Elgin, Illinois.

TABLE II—SERUM-LIPID DATA DURING SUCCESSIVE STUDY PERIODS
(Transitional data were omitted in calculating mean ± standard deviation. During each dietary period calculations were based only on steady-state data obtained in *n* successive determinations.)

Patient	Dietary fat	*n*	Steady-state data (mg. per 100 ml. serum)			
			Total cholesterol	Free cholesterol	Total phospholipids	Triglycerides
I 30 yr. M	Ad-libitum diet	3	504 ± 44	166 ± 17	423 ± 37	810 ± 114
	Corn oil	6	253 ± 12	..	257 ± 12	486 ± 62
	Menhaden oil	6	158 ± 5	48	169 ± 15	230 ± 45
	Corn oil	5	197 ± 11	67, 74	214 ± 13	435 ± 60
II 38 yr. F	Ad-libitum diet	3	499 ± 21	138 ± 2	388 ± 23	299 ± 8
	Corn oil	6	306 ± 7	82, 76	270 ± 13	194 ± 35
	Menhaden oil	5	305 ± 28	82, 84	234 ± 12	161 ± 17
	Corn oil	4	325 ± 5	89, 87	268 ± 8	182 ± 9

Skin xanthomata began to disappear within a month of starting oil feeding, and they continued to shrink throughout all experimental periods.

Patient II, a 38-year-old white female with hypercholesterolæmia and tendon xanthomata, also was free of symptoms or signs of atherosclerosis. She required 2250 calories per day (37 calories per kg.) to maintain her body-weight. "Steady-state" data from three dietary periods are listed in table II. The levels of total cholesterol, phospholipids, and triglycerides were not significantly different during the corn-oil and menhaden-oil periods. However, in all three test periods the levels of cholesterol and phospholipids were significantly lower than when taking an ad-libitum diet. There was no change in tendon xanthomata during the experimental study.

Changes in Serum-fatty Acids

The composition of the fatty-acid mixture of each lipid group in the serum of both patients was determined after equilibrium had been established in the menhaden-oil and in the second corn-oil dietary periods. The three serum-lipid ester groups (cholesterol esters, triglycerides, and phospholipids) were isolated by preparative chromatography on silicic-acid columns (Hirsch and Ahrens 1958) from chloroform/methanol extracts of 8–16 ml. of serum (Folch et al. 1951). The methyl esters of the fatty acids were formed and isolated (Stoffel et al. 1958b) and were analysed by gas/liquid chromatography on Apiezon M and Reoplex 400 columns.

The fatty-acid compositions in the right side of table I are calculated as percentages of the total mixture in each ester group. When corn oil replaced menhaden oil as the sole dietary fat, the fatty acids of all serum-lipid groups were strikingly affected. In both patients the saturated acids and C_{20-22}-polyenes, which were characteristic of menhaden oil, were correspondingly higher in all lipid groups during the menhaden-oil diet. On the other hand, in both patients during corn-oil diets the C_{18}-dienes increased considerably in all groups.

At the bottom of table I are shown the levels of the three serum-lipid groups in the serum at the designated times. From these data the content of individual acids in each group was calculated (e.g., mg. of 16 : 0 per 100 ml. serum in the cholesterol-ester fraction). Five acids comprised more than 80% of the total in each group; changes in these acids are shown graphically in fig. 2. The ratios of the five major acids to each other in the cholesterol esters were very similar in the two patients in comparable feeding periods (i.e., patterns of cholesterol-ester fatty acids during corn-oil diets in patient I versus patient II). Likewise, the patterns of acids in the phospholipids also were similar in the two patients in respective feeding periods, but they differed considerably from the cholesterol-ester patterns. There were striking dissimilarities in the distribution of major acids in the triglyceride fractions of the two patients on the two diets.

In both patients the fatty-acid mixtures of the three ester groups showed distinctive inter-group differences during the two dietary regimens.

Phospholipids.—About 50% of the acids were saturated in three of four dietary periods, and when patient I was on menhaden oil nearly 70% of the acids were saturated. The phospholipids appear to have the most unchanging fatty-acid pattern of any serum-lipid group. The triglycerides and cholesterol esters, however, more strongly mirror the changes in the dietary fats.

Cholesterol esters.—Of the three ester groups, the cholesterol-ester fatty acids showed the smallest proportion of saturated acids in three of four periods; hence the highest calculated

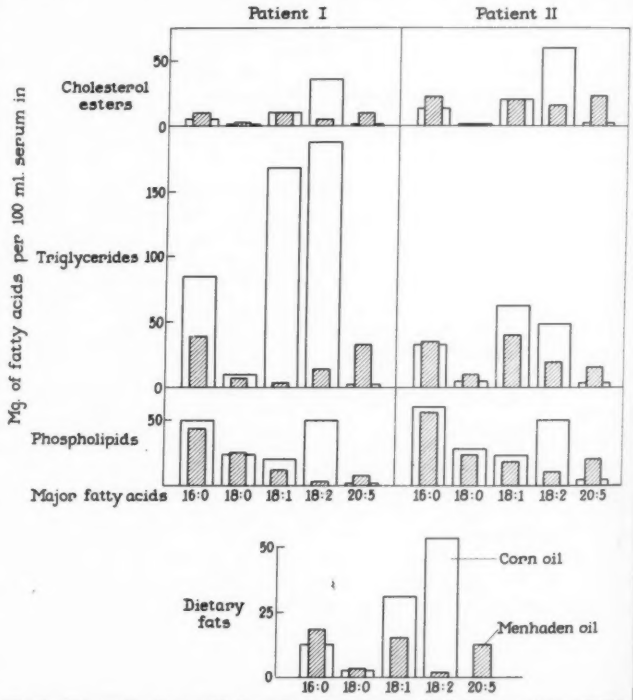

Fig. 2—Five major fatty acids in each of three serum-lipid groups, when patients I and II were given menhaden oil or corn oil as the sole dietary fat. Results are expressed as mg. of each acid in each group, per 100 ml. serum.

This quantitative representation differs from that in table I, where all fatty acids are expressed as % of total acids of each serum-lipid group. At the bottom, the compositions of the two dietary fats are compared. The 5 major acids made up 99% of the acids in corn oil. But in menhaden oil these same acids comprised only 50% of the total acids; four other major components, not shown (14 : 0, 16 : 1, 18 : 4, and 22 : 6), totalled 29%, while at least 35 minor acids made up the remaining 21%.

iodine value. Moreover, during respective dietary periods this fraction contained a higher proportion of linoleic acid than was present in the corn oil (table I). There was also a higher proportion of C_{20}-pentaenes and C_{20}-tetraenes than was present in menhaden oil, but in contrast C_{22}-pentaenes and C_{22}-hexaenes of menhaden oil did not appear in the cholesterol-ester fatty acids.

Triglycerides.—The acid mixtures of the triglycerides were altered by the two dietary fats, particularly in patient I. There was considerable resemblance between the triglyceride fatty acids in patient I to corn oil, and in patient II to menhaden oil during those dietary periods. The C_{22}-polyenes appeared more strikingly in the triglycerides than in the cholesterol esters.

TABLE III—SUMMARY OF DIETARY EXPERIMENT

—	Characteristics of dietary fats			Effect on serum-lipids	
	E.F.A.	Sterols	Iodine value	Patient I	Patient II
Corn oil	54%	1·5%	126	↓↓	↓
Menhaden-body oil	4%	<0·2%	179	↓↓↓	↓

In the four dietary periods, acids shorter in chain-length than C_{14} formed an insignificant proportion of all ester groups. Although myristic acid (14 : 0) constituted 7% of the menhaden-oil fatty acids, it made up only a small part of the serum-fatty acids. The predominance of palmitic acid over stearic acid was striking in the cholesterol esters and triglycerides; however, in the phospholipids, stearic acid assumed much greater importance in all dietary periods. The odd-numbered acids in menhaden oil did not appear in the serum in significant concentrations.

From table I it is apparent that all serum-ester groups are influenced by the pattern of acids in the dietary fat. However, we lack precise knowledge of the turnover of dietary fatty acids in man, and it would be misleading at this time to assume that alterations in fatty-acid patterns in the serum indicate significant changes in utilisation of the individual acids. Moreover, the differences in triglyceride fatty acids of the two patients may reflect a fundamental metabolic difference between patients with hyperlipæmia and those with hypercholesterolæmia.

Discussion

Despite efforts to produce a completely bland oil, the menhaden oil was somewhat distasteful. Nevertheless, amounts of oil equal to 40% of the total calories (100 to 125 g. per day) incorporated in the liquid mixture of protein, carbohydrate, and water caused no gastro-intestinal complaint. The isocaloric substitution of menhaden oil for the bland and relatively tasteless corn oil produced no change in total body-weight; presumably both oils were equally well absorbed. Physical activity and sense of well-being also were unchanged.

The content of E.F.A. in the menhaden oil used in these experiments was found to be exceedingly low by two independent methods. The chromatographic analyses defined the upper limits of the levels of linoleic and arachidonic acids. However, since menhaden oil might contain essential acids other than these two (Thomasson 1956), it was necessary also to determine the E.F.A. activity of this oil biologically. The bioassay data are compatible with the chemical data, showing a very low titre of E.F.A., in agreement with values found previously (Thomasson 1953) for samples of menhaden and other marine oils.

The results of our dietary tests in two patients are summarised in table III. Since it is seen that isocaloric substitution of E.F.A.-poor menhaden oil for E.F.A.-rich corn oil produced as low or lower levels of serum-lipids, it may be concluded that the presence of E.F.A. is not required to produce these serum-lipid alterations. Findings reported by other laboratories are consistent with the present results: pilchard oil fed by Bronte-Stewart et al. (1956), sardine oil used by Keys et al. (1957), and whale oil tested by Malmros and Wigand (1957) caused significant depressions in levels of serum-cholesterol. Although the highly unsaturated fats used in those tests were not completely characterised, chemically or biologically, it is probable (Thomasson 1956) that they had a low E.F.A.-content. Our results fail to confirm Beveridge's postulate (Beveridge et al. 1958) that the effectiveness of corn oil in lowering serum-cholesterol levels is mainly due to its sitosterol content (about 1·5%). The menhaden-body oil used in this study contained only negligible amounts of sterols, yet the serum-lipid effects were comparable, whether menhaden oil or corn oil was given.

Conclusions

A menhaden-body oil, acceptable for human consumption in large quantities over a long period of time, was prepared for use in dietary experiments on a metabolic ward.

The content of essential fatty acids in the oil, determined chemically and by bioassay, was found to be less than 4% of the total fatty acids. The content of total non-saponifiable material was less than 0·2%.

When menhaden oil was substituted isocalorically for corn oil in the diet of two patients (one with hyperlipæmia, the other with hypercholesterolæmia) serum levels of cholesterol, phospholipids, and triglycerides remained depressed. The fatty-acid patterns of all three ester groups of the serum-lipids were considerably affected by the strikingly different composition of the two dietary fats.

The effects on serum-lipid levels were unrelated to the essential-fatty-acid and sterol contents of the dietary fats under consideration.

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MALABSORPTION AND JEJUNAL ULCERATION DUE TO GASTRIC HYPERSECRETION WITH PANCREATIC ISLET-CELL HYPERPLASIA

W. H. J. SUMMERSKILL *
M.A., D.M. Oxon., M.R.C.P.

LATE SENIOR REGISTRAR, DEPARTMENT OF GASTROENTEROLOGY, CENTRAL MIDDLESEX HOSPITAL, LONDON, N.W.10

THE association between gastric hypersecretion, fulminating peptic ulceration, and pancreatic islet-cell adenoma has been confirmed as a clinical syndrome in some fifty cases (Zollinger and Ellison 1955, Donaldson et al. 1957, Zollinger and McPherson 1958). Gastric hypersecretion is evident from the aspiration of 2 litres or more of strongly acid juice in twelve hours at night, while the peptic ulceration is often atypical, involving particularly the jejunum and lower duodenum, and often recurring after partial gastric resection and gastrojejunal anastomosis (Ellison 1956).

The nature of the pancreatic lesion and its relationship to the disorder of gastric secretion are less certain: a non-beta-cell adenoma, which is sometimes ectopic and often malignant, is found most frequently. Other endocrine adenomas, including beta-cell pancreatic insulinomas, have been occasional findings (Donaldson et al. 1957); but the Zollinger-Ellison syndrome can be clearly distinguished on clinical grounds from the more remote association of pancreatic hyperinsulinism with peptic ulcer (Janowitz and Crohn 1951).

In most cases so far described, recognition of the syndrome has been retrospective—after gastric surgery or at necropsy—and little has been known about preoperative gastrointestinal function. The following case is reported because detailed observations were possible both before and after operation.

Clinical Case-report

History

From 1954 a 35-year-old engineer had periods of epigastric pain, worse at night and before meals and relieved by food and antacids. Between January to June, 1958, the pain became more persistent and there was a weight-loss of 22 lb. The patient had melæna in 1955, 1957, and on several occasions in 1958, and diarrhœa—several pale, loose, offensive motions daily—grew worse during the latter two years.

In March, 1958, no abnormality was found on the barium meal, but laparotomy was performed because of recurrent gastrointestinal bleeding. The proximal 7 in. of jejunum looked inflamed and thickened, and was therefore resected. The naked-eye appearances suggested Crohn's disease, but pathological examination showed three chronic peptic ulcers with associated inflammation.

The symptoms returned soon after operation, and a large peptic ulcer of the jejunum was demonstrated radiologically (fig. 1). The patient was transferred to the Central Middlesex Hospital, and, on the basis of investigations to be described, he was diagnosed as a case of the Zollinger-Ellison syndrome.

Operation

At laparotomy no pancreatic tumour or ectopic pancreatic tissue could be identified; but a large chronic ulcer was found at the duodenojejunal flexure, together with five smaller chronic ulcers in the upper jejunum and numerous bleeding erosions in the duodenum. The whole stomach, the tail of the pancreas, the distal duodenum, 35 cm. of the upper jejunum, and the spleen were resected. A Roux-loop of jejunum and proximal duodenum was anastomosed en-Y to the œsophagus.

* Present address : Mayo Clinic, Rochester, Minnesota, U.S.A.

Histological Findings

Stomach.—There were deep gastric glands and a relative increase in oxyntic cells.

Jejunum.—The mucous membrane was hyperplastic with thick folds. Five chronic peptic ulcers (average diameter 0·5cm.) and several areas of hæmorrhage were found. The ulcers had necrotic floors and granulomatous bases, and the circular muscle-coat had been destroyed. Elongated villi and deep glands showed numerous mitotic cells, and inflammatory cells had infiltrated the whole thickness of intestine.

Fig. 1—Barium meal showing a large ulcer in the upper jejunum.

Pancreas.—The tail of the pancreas weighed 65 g. There was no evidence of tumour or pancreatitis. The islets were very prominent and more numerous than normal. Gomori's aldehyde-fuchsin stain showed normal beta-cells; but the post-coupled benzylidine reaction, which demonstrates the tryptophan component of glucagon, suggested increased alpha-cell activity. This was compatible with patchy hyperplasia of the alpha-cells.

Methods of Investigation

Before operation samples of gastric or intestinal contents were aspirated on different occasions from the angulus of the stomach, the distal half of the duodenum, and the first 20–30 cm. of the jejunum. Radio-opaque single-lumen rubber tubes were used (fig. 2). Sixteen days after operation—when the patient was apyrexial, ambulant, and taking a normal diet—specimens were taken from a point 5–10 cm. below the anastomosis.

Basal secretions were collected after overnight fasting for one-hour periods on different mornings from each site. Subsequently, one-hour specimens of gastric secretion (after stimulation with histamine, 2·0 mg. subcutaneously) or lower duodenal contents (after stimulation with secretin or pancreozymin, 1·5 units per kg., intravenously) were obtained. After preliminary emptying, these specimens were aspirated by a continuous-suction pump and manually at intervals of five to

Fig. 2—Tube for aspiration of the jejunum in position. Arrows mark the sites from which gastric, lower duodenal, and upper jejunal samples were withdrawn.

TABLE I—BASAL AND STIMULATED GASTRIC SECRETION BEFORE OPERATION COMPARED WITH DUODENAL AND JEJUNAL CONTENTS AND WITH POSTOPERATIVE SECRETION BELOW THE ANASTOMOSIS

Aspiration (per hour)	Preoperative				Postoperative results	
	Gastric		Lower duodenal	Upper jejunal	Below the anastomosis	
	Basal	Histamine stimulation			Basal	Histamine stimulation
Volume (ml.)	512 (*77*)	625 (*135*)	1070	950	28	32
pH	1·1 (*>1·5*)	1·1 (*1·7*)	1·3 (*>5·0*)	1·4 (*6·0*)	7·3	7·3
Free HCl (mEq/litre)	69·3 (*2·0*)	85·8 (*19·1*)	65·2 (*0*)	49·4 (*0*)	0	0
Pepsin (units)	3789 (*≤200*)	5433 (*≤1000*)	9737 (*0*)	7695 (*0*)	0	0

Normal values are given in parentheses.

fifteen minutes. Collections for analysis were made at fifteen-minute intervals. At other times—while the patient was ambulant and taking standard hospital meals with antacids when necessary—aliquots were aspirated hourly from each site during twenty-four-hour periods of continuous intubation.

Free hydrochloric acid, bicarbonate, pH, blood-glucose, and fæcal fat were estimated by standard methods. Pepsin was measured by the method of Hunt (1948), but using tyrosine as an indicator; and the technique described by Sircus (1954) was used for uropepsinogen. Tryptic activity was determined by the procedure recommended by Harrison (1957). The " normal " values quoted reflect general experience in this department and agree with those of Atkinson and Henley (1955) and Sircus (1958). The pH of normal upper-intestinal contents is based, in particular, on the report of Borgström et al. (1957).

Results of Investigation

The patient's preoperative hæmoglobin was 14·1 g. per 100 ml. (95%), his white-cell count was 7000 per c.mm. and his erythrocyte-sedimentation rate (Westergren) 13 mm. Occult-blood tests in the stools were strongly positive. His urine, serum-electrolytes, and liver-function tests showed no abnormality. The urinary excretion of 5-hydroxyindoleacetic acid was 4·1 mg. in twenty-four hours (within normal limits).

Gastric Secretion

Gastric secretion, grossly abnormal before operation, even under basal conditions, showed a relatively small increase in volume, acid, and pepsin after histamine (table I). The increased basal secretion was associated with a very high uropepsinogen excretion (535 units per twenty-four hours; normal <150 units) and with free hydrochloric acid and peptic activity in the lower duodenum and upper jejunum (table I). The fact that there was more pepsin in the duodenum and jejunum than in the stomach suggests that even continuous suction could not cope with all the gastric juice.

Despite regular meals and the unrestricted antacids (which account for the drop in acidity at night when pain was more severe) the pH of the gastric, lower duodenal, and upper jejunal contents remained strongly acid (table II). The stool pH was normal (7·5).

Acid-pepsin secretion was abolished by the operation, and there was no longer any response to histamine (table I). The pH below the anastomosis remained between 5·0 and 8·0 (table II).

TABLE II—TWENTY-FOUR-HOUR PH OF GASTRIC, LOWER DUODENAL, AND UPPER JEJUNAL CONTENTS

Time	Preoperative			Postoperative
	Stomach	Lower duodenum	Upper jejunum	Below the anastomosis
Noon	1·40	1·30	1.60	7·35
1.00 p.m.	..	1·45	2·50	..
2.00	1·40	1·40	1·60	5·80
3.00	..	1·30	2·20	..
4.00	2·20	1·30	2·05	5·30
5·00	1·30	..	2·60	5·15
6·00	1·25	1·75	3·60	..
7.00	1·25	2·40	3·80	..
8.00	1·70	1·45	2·80	5·35
9.00	1·25	1·25	1·60	5·40
10.00	1·10	1·65	1·65	5·40
11.00	1·40	1·70	2·10	7·50
Midnight	1·20	2·35	2·75	6·50
1.00 a.m.	1·20	6·15	4·50	..
2.00	1·15	5·90	5·40	..
3.00	1·60	2·75	..	7·65
4.00	1·20	1·40	5·35	..
5.00	1·40	1·40	..	..
6.00	1·15	5·05	1·90	6·25
7.00	1·15	1·50	1·60	5·80
8.00	1·15	1·30	1·45	6·40
9.00	2·95	1·60	1·80	7·15
10.00	1·15	1·30	1·70	..
11.00	3·95	..	1·50	7·30
Normal range	1·50–6·00	5·00–7·00	6·00–8·00	—

TABLE III—PANCREATIC SECRETION IN RESPONSE TO PANCREOZYMIN AND SECRETIN

Duodenal contents (per hour)	Preoperative				Postoperative	
	Secretin		Pancreozymin		Pancreozymin	
	Control	After intravenous injection	Control	After intravenous injection	Control	After intravenous injection
Volume (ml)	1070	945	..	..	81	71
pH	1·30–1·45	1·25–1·50	1·30	1·30	7·50–8·00	7·00–9·00
H_2CO_3 (mEq./per litre)	5·8	10·2	4·8	3·5	44·7	32·9
Trypsin	negative	negative	negative	negative	positive 1/100	positive 1/100
Bile (0–++++)	0	Trace	0	0	++	+

Pancreatic Function

Before operation intravenous secretin caused but a slight, transient increase in duodenal bicarbonate and bile concentration. The pH remained strongly acid, and no tryptic activity could be demonstrated in the duodenal juice either before or after intravenous pancreozymin. After operation the pH was alkaline just below the anastomosis and trypsin was present in very high concentrations both before and after stimulation. The aspirated fluid was bile-stained, especially during the control period.

The glucose-tolerance curve before operation showed a slight delay in the return of the blood-sugar to the fasting level (90; 140, 150, 118, 80 mg. per 100 ml.). After operation the changed tolerance curve (110; 225, 290, 235, 165 mg. per 100 ml.) was attributed to the total gastrectomy and partial pancreatectomy.

Fat Absorption

Before operation the patient had two or three pale, loose, offensive motions daily; and his fat excretion was 82 g. in three days on a standard ward diet containing 100 g. fat daily. The diarrhœa improved after operation,

Fig. 3—Barium follow-through before operation, showing steatorrhœa pattern.

Fig. 4—Barium follow-through after operation, showing normal pattern.

the stools became firmer, and darker and fæcal fat loss was reduced to 56·5 g. in three days. Similarly, the steatorrhœa pattern shown preoperatively on the barium follow-through films changed to normal (figs. 3 and 4).

Intestinal Motility

In the preoperative period rapid emptying made it difficult to outline the stomach and duodenum with barium: it reached the ileocæcal valve within two hours and outlined the entire colon within three hours. After the operation intestinal motility diminished: whereas before a swallowed carmine-dye marker took three hours to appear in the stool, it now took thirteen hours.

Discussion

Though peptic ulceration of the upper jejunum associated with gastric hypersecretion is "almost pathognomic" of the Zollinger-Ellison syndrome (Zollinger and McPherson 1958), the patient here reported had no pancreatic adenoma. Zollinger and McPherson (1958) suggested, however, that diffuse hyperplasia of the islet-cells (rather than a discrete adenoma) could be the pancreatic component of the syndrome—a condition analogous to hyperparathyroidism. The findings in the present case support this view. Differentiation between various types of islet cells presents many technical difficulties; but it is widely believed that, as in the patient here presented, the syndrome involves the alpha-cells. The actual ulcerogenic factor is more obscure; but glucagon, which is produced by the alpha-cells, and which was originally suspected by Zollinger and Ellison (1955), has yet to be excluded. When no localised lesion is found, total gastrectomy and hemipancreatectomy have been recommended, and in the present case this operation dramatically improved gastrointestinal function and relieved all symptoms.

Gastric secretion in the syndrome can exceed 9 litres in twenty-four hours (Donaldson et al. 1957). Hourly aspirations in the present case were over 500 ml., and the aspirates contained large quantities of pepsin and free hydrochloric acid. The relatively small increase in response to histamine suggests that the gastric mucosa was already almost maximally stimulated and the pH was scarcely influenced by meals or antacids. The urinary uropepsinogen levels were very high, as in the case described by Donaldson et al. (1957).

The preoperative steatorrhœa, diarrhœa, and lack of pancreatic enzyme activity were first attributed to pancreatic deficiency; but the improvement after surgical treatment, and the appearance of the pancreas at laparotomy and on histological examination, called for an alternative explanation. In the lower duodenum and upper jejunum the pH is normally between 5·0 and 8·0 (Borgström et al. 1957), and there is no free hydrochloric acid or peptic activity. Gastric hypersecretion can, however, alter these conditions: preoperative intubation studies in the present case showed free hydrochloric acid and peptic activity at both levels, persisting for much of the twenty-four hours of the day. Such abnormal acid-pepsin concentration could well account for the ulceration as the jejunum is particularly susceptible to continued acid-pepsin action.

Whereas before operation pancreozymin and secretin injections did not raise the duodenal trypsin, bicarbonate, or bile concentrations, results of the postoperative estimations were normal. The optimum pH for tryptic activity is 7·0–9·0, while enterokinase, which activates trypsin, has an optimum range of 5·0–6·0 (Hawk et al. 1954). The pH of small-intestinal contents before operation in this patient was thus too acid, and bicarbonate secreted by the pancreas and liver could not neutralise the large amounts of gastric acid. Trypsin, moreover, is destroyed by pepsin in acid solutions.

The disordered intestinal fat absorption and motility were also related to the gastric hypersecretion, although glucose absorption was unaffected. That the steatorrhœa improved and the radiological deficiency-pattern disappeared after operation was especially gratifying after total gastrectomy, hemipancreatectomy, and resection of the upper jejunum, any of which is liable to produce or aggravate malabsorption. In fact, the residual post-operative fat excretion was within the range that may follow total gastrectomy alone in a subject without previous steatorrhœa (Ellison 1955).

Fat absorption begins in the duodenum and is normally completed in the proximal 100 cm. of the jejunum, and pancreatic lipase is the most important agent in fat digestion (Borgström et al. 1957). Since, however, pancreatic lipase has an optimal pH of 7·0, fat digestion must have been depressed before operation by the acid milieu of the upper jejunum. Maynard and Point (1958) described a case in which steatorrhœa and diminished tryptic activity were similarly associated with gastric hypersecretion; one duodenal pH reading was 4·25; but in their patient most of the pancreas had been destroyed by tumour, so the basis of malabsorption was obscure.

Diffuse mucosal damage in the upper intestine, presumably due to acid-pepsin activity, was first diagnosed on aspiration biopsy and later confirmed on the surgical specimen. Theoretically, this could also have contributed to the malabsorption, with increased intestinal motility as an aggravating factor. Diarrhœa has been an early and prominent symptom in 7 probable cases of the Zollinger-Ellison syndrome, but steatorrhœa has not been reported

in them. In 4 patients severe diarrhœa was the main complaint; and it caused potassium depletion in 3 of these (Priest and Alexander 1957, Donaldson et al. 1957, Verner and Morrison 1958). The mechanism of this diarrhoea is obscure; but the improvement in the present case after operation, and the temporary improvement in Donaldson's patient after gastric aspirations, point to a direct link with gastric hypersecretion. It is possible that acid and pepsin have an irritant action in the small intestine.

Summary

A patient had multiple chronic peptic ulcers of the jejunum, gastric hypersecretion, and pancreatic islet-cell hyperplasia. Diarrhœa and steatorrhœa were prominent clinical features.

Gastrointestinal and pancreatic function were studied in detail both before and after operation. The findings are discussed in the light of current concepts of the Zollinger-Ellison syndrome. Grossly increased gastric secretion, leading to acid-pepsin activity in the upper intestine, could be held responsible for the peptic ulceration of the jejunum, for the steatorrhœa (by inactivating lipase), for the inactivation of trypsin, and for the diarrhœa.

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ISLET-CELL TUMOUR OF PANCREAS ASSOCIATED WITH PEPTIC ULCERATION

BRUCE PENDER
M.B. Lond., F.R.C.S.

SENIOR SURGICAL REGISTRAR, ST. GEORGE'S HOSPITAL, LONDON, S.W.1

SINCE the original paper by Zolliger and Ellison (1955) there have been more reported cases in which an islet-cell tumour of the pancreas, containing no β-cells, was associated with recurrent ulceration of the stomach and small intestine (Zolliger and McPherson 1958). At the World Congress of Gastroenterology in Washington last May, about 75 cases of the syndrome were confirmed. The one to be described has several unusual features.

Case-report

A man of 39 was admitted to St. George's Hospital (The Grove) complaining of diarrhœa, anorexia, and vomiting for three months. He was afraid to eat because of pain after meals, and he had constant pain in his left shoulder and scapular regions.

Past History

In May, 1951, he was admitted to another hospital with severe hæmatemesis for which an emergency partial gastrectomy (Polya type) was performed. Convalescence was uneventful.

In August, 1952, he returned to the same hospital with symptoms of a stomal ulcer. This was confirmed by gastroscopy. At operation the ulcer was found in the gastric remnant penetrating the diaphragm. It was excised and an abdominal vagotomy was performed. He remained well for a year.

In April, 1953, he again developed symptoms of a stomal ulcer. A third of the remaining stomach was resected and an anastomosis was performed.

When his gastric symptoms recurred in 1956 he was under treatment at the same hospital for anxiety neurosis. On gastroscopy three months earlier the gastric remnant had been normal. While under treatment he developed a swinging temperature and a raised erythrocyte-sedimentation rate. This was ascribed to an area of consolidation at the base of the left lung with a small effusion. He was treated with penicillin and recovered.

Present Illness

On admission on April 4, 1958, he appeared emaciated and complained of anorexia, vomiting after food, and pain in the left shoulder. A barium meal was equivocal, but it suggested a carcinoma in the stomach remnant. In view of his past history, however, he was given a period of medical treatment; and, on repeat X-ray examination, the gastric lesion was smaller. A tentative diagnosis of recurrent stomal ulceration with islet-cell tumour was made.

Investigations

His hæmoglobin was 71%, the white-cell count 7800, and the erythrocyte-sedimentation rate 20 mm. He had occult blood in his stools. A test-meal showed a large quantity of resting juice and high acid. Sigmoidoscopy was normal: gastroscopy was unsuccessful. On screening, the left leaf of the diaphragm was immobilised, and it was felt that besides the recurrent ulceration he might have a subphrenic abscess. He was transfused and his hæmoglobin rose to 80%.

Operation

On June 10 he was explored through a thoracoabdominal incision; and it soon became apparent that there was an ulcer, about an inch in diameter, on the anterior wall of the small stomach remnant. The ulcer had penetrated the diaphragm and was firmly adherent to the transverse colon, but there was no fistula. A total gastrectomy, using a loop of jejunum, and splenectomy, combined with a 4-inch enteroenterostomy was performed. The enteroenterostomy was carried up almost to the anastomosis. At the junction of the body and tail of the pancreas a tumour, 1 cm. in diameter, was felt. It was resected. The abdomen was closed with drainage. The patient recovered from the operation extremely well, and he was taking a light fortified diet on the fifth day supplemented by injections of vitamin B_{12} and folic acid. He gained 3 lb. within the first three weeks of his convalescence.

Histology

The stomach remnant contained an ulcer 1 cm. in diameter, the edge of which was œdematous and thickened. The anastomosis in the jejunum was also ulcerated.

The pancreatic tumour was a well-encapsulated, benign islet-cell adenoma. Special stains showed β-cell granules in the normal islets but no granules in the tumour.

Family History

The patient's wife, when his condition was explained to her, said that their only child, a girl now aged 12, had been diagnosed as an epileptic in 1953. But her fainting attacks could be controlled or cured by food; and on further investigation, she had been found to have hyperinsulinism. A benign islet-cell adenoma of the pancreas had been discovered and removed and she had been free from symptoms ever since. β-cell granules were demonstrated in the tumour.

Summary

A man who had had repeated operations for recurrent peptic ulceration was eventually treated by total gastrectomy and removal of a benign non-insulin-secreting islet-cell tumour of the pancreas. His daughter had a benign islet-cell tumour removed for hyperinsulinism at the age of 7.

I am indebted to Prof. T. Crawford and his department at St. George's Hospital for their cooperation. I should also like to thank Mr. M. F. Nicholls for allowing me to treat and publish this case.

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TESTOSTERONE IN DEFECTIVE SPERMATOGENESIS

A. W. SPENCE
M.A., M.D. Cantab., F.R.C.P.
PHYSICIAN-IN-CHARGE OF A MEDICAL UNIT AND OF THE ENDOCRINE CLINIC

V. C. MEDVEI
M.D. Vienna, M.R.C.P.
ASSOCIATE CHIEF ASSISTANT TO THE ENDOCRINE CLINIC
ST. BARTHOLOMEW'S HOSPITAL, LONDON, E.C.1

MORE than twenty years ago it was shown that the administration of androgens prevents degeneration of the seminiferous tubules and maintains spermatogenesis in hypophysectomised animals (Walsh et al. 1934, Nelson and Gallagher 1936). It was concluded that one of the physiological functions of testosterone is to promote spermatogenesis, and its use was advocated for the treatment of defective spermatogenesis in man. It should be borne in mind, however, that the germinal epithelium of the hypophysectomised animal and that of the patient with defective spermatogenesis are not comparable, except when the defect is caused by hypopituitarism of moderately recent onset. In hypophysectomised animals the testes are atrophic merely through lack of stimulation, and they will respond to treatment provided it is not too long delayed. But in patients with testicular atrophy the germinal epithelium fails because of an intrinsic pathological process and may thus be incapable of responding to stimulation. Furthermore, in patients with defective spermatogenesis for whom testosterone is advocated there is usually no evidence of testosterone deficiency.

A further difficulty in the treatment of defective spermatogenesis with testosterone is the dosage. In the normal subject, because testosterone is produced locally by the Leydig cells of the interstitial tissue, it can act directly on the germinal epithelium in high concentration. On the other hand, the intramuscular injection of a total of 75 mg. of testosterone propionate per week is liable to depress spermatogenesis by suppressing the secretion of pituitary gonadotrophin (Rubinstein and Kurland 1939, McCullagh and McGurl 1940, Heckel 1940). Hence fairly small doses of testosterone have been recommended to avoid this effect on the pituitary gland, but it is doubtful whether such doses produce the local concentration that is normally present in the testes.

Heckel et al. (1951, 1952) observed in patients with moderate oligospermia that the azoospermia produced by treatment with high doses of testosterone propionate for three or four months was often followed by a rebound phase in which the sperm-counts gradually rose until they exceeded the pretreatment level. Out of 36 patients so treated five pregnancies resulted. Swyer (1953), on the ground that the continuous administration of testosterone in low dosage might stimulate spermatogenesis or improve sperm-motility, treated oligospermia by the subcutaneous implantation of pellets of testosterone and so produced fertility in 20 of 56 sterile men. To avoid the depressive effect of continuous treatment with androgens, Harvey and Jackson (1957) gave the husband methyltestosterone 10 mg. daily from the sixth to the sixteenth day of the wife's menstrual cycle for four to twelve cycles. In 35 (38%) of 93 cases the wife became pregnant within two years.

In this report we describe our experience with preparations of testosterone in the treatment of men with defective spermatogenesis during the years 1950–58. The methods employed were (1) sublingual administration of methyltestosterone, (2) intramuscular injection of high doses of testosterone propionate to bring about the rebound phenomenon, (3) intramuscular injection of a

TABLE I—RESULTS WITH METHYLTESTOSTERONE THERAPY

Case no.	Initial semen examination				Daily dose (mg.)	Duration (mos.)	Final semen examination				Pregnancy	Estimated time of conception (mos. after starting treatment)
	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)			Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)		
1	2·5	8·0	10	0	10 25	5 7	2·7 2·8	4·5 4·0	50 30	0 0	+	11
2	2·7	12·0	30	0	5	8	3·0	32·0*	50	0	+	7
3	2·0	8·0	25	0	5	9	2·0	2·0	<1	0	0	..
4	2·7	12·0	1	6	5 15	9 2	3·3 2·9	15·0 13·0	25 12	10 4	0	..
5	2·8	18·0	10	0	5	6	2·0	6·0	20	Few	0	..
6	2·5	5·0	25	0	10 25	4 9	4·5 8·1	1·0 7·0	20 60	0 0	0	..
7	2·0	3·0	<1	0	10	7	2·5	5·0	10	0	0	..
8	2·0	4·0	5	0	5 25	7 9	2·5 2·0	18·0 12·0	45 25	0 0	0	..
9	3·0	0·25	2	0	15 5 20	3 12 12	6·3 3·5 3·0	7·5 8·0 6·0	5 <1 <1	0 0 0	0	..
10	2·5	2·0	<1	0	5	14	2·0	45†	70	Few	+	18

* At the end of 5 months. † At the end of 10 months.

crystalline suspension of testosterone isobutyrate, and (4) implantation of pellets of testosterone.

Material and Methods

59 patients with defective spermatogenesis (excluding those with eunochoidism, hypopituitarism, and azoospermia) attended our clinic, but 29 of these either refused treatment or abandoned it in the early stages. Of the remaining 30 patients, none had any evidence of general disease, all had normal secondary sexual characteristics, and all had testes which appeared normal in size.

Two or three specimens of semen were examined before treatment was begun and the patient was instructed to abstain from intercourse during the four days before each specimen was produced. The highest sperm-count was taken as the pre-treatment figure. Specimens were obtained in the laboratory by masturbation into a warm petri dish, and were examined within an hour for volume, density, and percentages of motile spermatozoa and abnormal forms. Viability was not investigated. In assessing the quality of seminal fluid the figures taken as the minimal "normal" were those used by Davidson (1949)—namely, volume 1·5 ml., density 40 million per ml., motility 40–50%, abnormal forms not in excess of 40%. Seminal examinations were usually made at intervals of one, two, or three months after treatment was started, but occasionally the intervals were longer if the patient defaulted (in the tables not all the counts are inserted). Patients were advised to have intercourse especially at about the time of ovulation.

At first testicular biopsies were performed on some patients, but this investigation was later abandoned because azoospermia, which is due to a bilateral block of the ducts or epididymis or to complete failure of spermatogenesis, was considered to be unresponsive to treatment, and because oligospermia is rarely caused by a block.

Methyltestosterone

10 patients with oligospermia were treated with methyltestosterone in sublingual doses of 5 to 25 mg. daily for periods that ranged from four to sixteen months, except 1 (case 9) in whom treatment was given for over two years. Testicular biopsies (Mr. A. W. Badenoch) on 3 patients had the following histological appearances:

Case 4.—The right testis showed atrophy of some tubules, but in others spermatogenesis had proceeded as far as the formation of young spermatozoa. The left testis showed moderate atrophy, only a few spermatogonia persisting; there was no evidence of spermatogenesis. Interstitial changes were minimal. (Dr. J. G. Cunningham)

Case 6.—The right testis showed all stages of spermatogenesis, though spermatids and spermatozoa were less in evidence than the cells of the earlier stages. The basement membrane of the tubules showed some hyaline thickening. The left testis showed normal spermatogenesis at all stages. (Dr. Cunningham)

Case 8.—The right testis showed normal tubules with frequent mitoses in the spermatocyte stages, but spermatids and mature spermatozoa appeared rather infrequently for the patient's age (27 years). The left "testis" showed only fibrous and adipose tissue with no sign of testicular architecture. (Dr. R. J. R. Cureton)

Results

In 7 patients there was no appreciable change in the quality of the semen. In case 2 the sperm-count rose from 12 million per ml. to 32 million, and the motility from 30% to 50%. In case 10 the sperm-count of 2 million per ml. rose to 45 million and the motility from almost nil to 70%. In case 4 the motile forms increased from 1% to 25%, the density remaining practically unchanged. In case 8 the initial sperm-count of 4 million per ml. rose to 18 million, and the motility from 5% to 45% (table I).

The wives of 3 patients (30%) became pregnant—in case 1 with a spermatozoal density of 4 million per ml. and 30% motility, in case 2 with a density of 32 million and 50% motility two months before conception, and in case 10 with a density of 45 million and 70% motility eight months before conception. Case 10 stopped treatment of his own accord four months before conception, and eight months before conception he ceased attending the clinic for semen examinations.

Rebound Phenomenon

To determine whether the rebound phase could be produced, testosterone propionate was injected intramuscularly in doses of 50 mg. three times weekly for twelve weeks, except in 3 patients (cases 11, 12, and 18) who were unable to attend more than twice a week; case 11 attended for only six weeks. This group consisted of 13 patients. 2 patients (cases 17 and 18), whose seminal analyses were within the normal range, perhaps should not have been included, but as their wives had been passed as normal we gave them treatment to see what

TABLE II—RESULTS OF GIVING TESTOSTERONE PROPIONATE 50 MG. INTRAMUSCULARLY

Case no.	Initial semen examination				Frequency of injections (per week)	Duration of therapy (weeks)	Later semen examinations					Pregnancy	Estimated time of conception (mos. after starting treatment)
	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)			Time from start of treatment (mos.)	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)		
4	2·7	14·0	65	6	3	12	3	2·5	0	..	..	0	..
6	8·1	7·0	60	0	3	12	1	2·0	0	..	..		
							4	2·5	1·5	10	0		
							9	4·0	7	30	0		
							14	2·5	7	20	0		
							18	3·5	1	40	0	+	15
7	2·5	5·0	10	0	3	12	3	2·0	1	<1	0		
							6	3·0	4	<1	0	0	..
8	2·0	2·0	<1	0	3	12	3	3·0	9	<1	0		
							4	2·5	32	40	0		
							6	3·0	40	38	0		
							8	4·0	14	40	0		
							10	2·5	1	<1	0		
							13	3·0	10	30	0	0	..
9	3·0	6·0	<1	0	3	12	3	2·0	0	..	..		
							6	2·0	7	<1	0		
							10	3·0	6	10	0		
							13	3·0	9	15	0		
							16	2·5	3	<1	0	0	..
11	2·0	5·2	62	18	2	6	2	3·5	4	<1	0	+	2½
12	2·0	6·0	50	0	2	12	3	1·5	<1	0	0	+	4
13	3·5	26·0	30	0	3	12	2	2·5	0	..	..		
							3	3·5	0	..	..		
							11	4·5	8	80	0	+	12
							14	3·0	14	25	0	+	27
14	4·0	11·0	60	Few	3	12	3	3·5	0	..	..		
							7	3·5	6	<1	0		
							12	4·8	16	7	0		
							15	2·0	12	15	0	0	..
15	2·0	6·0	10	0	2	12	3	3·0	11	30	0		
							4	1·5	3	<1	0		
							7	3·0	17	30	0		
							9	2·0	8	20	0		
							11	2·5	7	10	0		
							14	2·5	42	25	0		
							17	3·0	36	10	0	+	17
16	2·5	11·0	25	0	3	12	3	3·0	2	<1	0		
							7	2·5	7	10	0		
							9	3·0	8	10	0	+	32
17	2·5	39·0	45	0	3	12	2	2·5	17	35	0		
							3	3·0	8	15	0		
							4½	4·0	3	40	0		
							6½	3·0	42	45	0		
							9½	2·5	56	40	0	0	..
18	3·0	42·0	30	0	3	12	2	2·5	0	..	..		
							3	2·3	0	..	..		
							10	2·9	32	30	0	+	10

might happen. 5 patients had been treated previously with methyltestosterone.

Results

Azoospermia was produced in 6 patients, although in case 18 the initial sperm-count was 42 million per ml. 1 patient (case 4), in whom azoospermia was produced, stopped attending at the end of the course of injections, but four years later we learned that pregnancy had not occurred. In only 5 patients did the sperm-count later rise above the pretreatment level, although in most cases seminal analyses were carried out for periods ranging from nine to eighteen months. In none of these was pregnancy achieved.

In 2 patients (cases 9 and 14) in whom azoospermia was produced the counts rose respectively from 6 million per ml. to 9 million thirteen months later, and from 11 million per ml. to 16 million a year later—neither being very impressive. In case 8, at the end of twelve weeks' treatment, the sperm-count rose from 2 million per ml. to 9 million, and three months later it was 40 million with 38% motility. In case 15 the initial count of 6 million per ml. fell to 3 million at the end of four months, but fourteen months after beginning treatment it

TABLE III—RESULTS OF GIVING INTRAMUSCULAR TESTOSTERONE ISOBUTYRATE 50 MG. PER MONTH FOR 6 MONTHS

Case no.	Initial semen examination				Later semen examinations					Pregnancy	Estimated time of conception (mos. after starting treatment)
	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)	Time after starting treatment (mos.)	Volume (ml.)	Count (millions per ml.)	Motility (%)	Abnormal forms (%)		
19	3·0	45	35	0	6	2·8	48	30	0	0	..
20	2·5	27	75	0	8	3·0	5	30	0	+	8
21	2·5	4	<1	0	8 10	3·5 3·0	1 1	10 <1	0 0	0	..
22	2	0	..	..	3 6	2·5 2·5	0 0	.. ..	.. ..	0	..
23	2·5	0	..	..	4	2·5	0	..	..	0	..
24	2·8	0	..	..	6 8	2·6 ..	0 0	.. ..	.. ..	0	..

rose to 42 million. In case 17 the initial count of 39 million per ml. fell to 3 million at the end of five months, but at the end of ten months it rose to 56 million (table II).

The wives of 6 patients (46%) became pregnant. The times of conception were:

Case 6—fifteen months after beginning treatment; the sperm-count was 7 million per ml. at fourteen months.

Case 11—about two months after starting treatment with testosterone propionate 50 mg. twice weekly which was continued for six weeks, the sperm-count being 4 million per ml., with only occasional motility.

Case 12—four months from the start of treatment; the sperm-count at three months was less than 1 million per ml.

Case 13—a year after starting treatment; the sperm-count was 8 million per ml. at eleven months.

Case 16—two years and eight months after starting treatment; the sperm-count at this time was unknown, though at the end of nine months it was only 8 million per ml.

Case 18—ten months from the start of treatment with a sperm-count of 32 million per ml. (table II).

Testosterone Isobutyrate

6 patients were treated by the intramuscular injection of a crystalline suspension of testosterone isobutyrate in doses of 50 mg. every four weeks for six months. The action is similar to that of an implant of testosterone in that there is a continuous slow absorption from the site of injection. Unfortunately a fair trial has not yet been made with this preparation because some patients were among those who abandoned treatment, 3 who continued had azoospermia, and 1 had a normal count. The quality of the semen was not improved; in fact in case 20 the sperm-count fell from 27 million per ml. to 5 million, but at this level his wife became pregnant (table III).

TABLE IV—RESULTS WITH TESTOSTERONE IMPLANTS

Case no.	Initial semen examination				Dose (mg.)	Later semen examinations					Pregnancy	Estimated time of conception (mos. after implantation)
	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)		Time after implantation (mos.)	Volume (ml.)	Count (million per ml.)	Motility (%)	Abnormal forms (%)		
25	1·5	0	..	..	200	5	1·5	0	..	..	0	..
26	5·5	12	40	0	100	2	3·0	4·0	<1	0	+	3
27	2·0	2·0	30	0	300	2 4	2·2 2·3	1·25 1·25	54 58	0 0	0	..
28	1·5	4	<1	0	300	2 4	2·0 1·5	4·0 1·0	20 0	0 0	0	..
29	3·5	0·08	5	0	300	2 4	2·0 2·0	3·0 1·0	<1 <1	0 0	0	..
30	2·5	Very few	0	0	300	2 4 6	2·5 2·5 2·5	0 1·0 <1	.. Most Most	.. 0 0	0	..

Testosterone Implants

6 patients were treated by the subcutaneous implantation of testosterone—case 25 with two 100 mg. pellets, case 26 with one 100 mg. pellet, and cases 27–30 with three 100 mg. pellets. The pellets are effective for about four months. Case 25 had azoospermia, and biopsies of the testes showed similar changes; all stages of spermatogenesis could be identified in some places, but in most tubules only the earlier stages were present, and many spermatocytes showed vacuolation and nuclear degeneration. 4 patients (cases 27–30) had very low sperm-density and poor motility.

Results

In 2 patients only was there any improvement in the quality of the semen. In case 29 the sperm-count rose from 80,000 per ml. to 3 million with no change in motility, and in case 30 from 12 spermatozoa in 40 fields

TABLE V—CONDITION OF SEMEN NEAR TIME OF CONCEPTION

Case no.	Volume (ml.)	Count (millions per ml.)	Motility (%)	Abnormal forms (%)	Time of count (mos. before conception)	Treatment
1	2·8	4	30	0	†	Methyltestosterone 25 mg. daily
2	3·0	32	50	0	2	Methyltestosterone 5 mg. daily
10	2·0	45	70	Few	8	
6	2·5	7	20	0	1	Testosterone propionate 50 mg. 3 times per week for 12 weeks
13	2·5	10	45	0	1	
18		32	30	0	†	
12	1·0	<1	None	0	1	Testosterone propionate 50 mg. 2 times per week for 12 weeks
15	3·0	36	10	0	†	
11	3·5	4	<1	0	½	Testosterone propionate 50 mg. 2 times per week for 6 weeks
20	3·0	5	30	0	†	Testosterone isobutyrate 50 mg. monthly for 6 months
26	3·0	4	<1	0	1	Testosterone implant of 200 mg.
32	2·0	7	25	0	1	None
33	1·5	0	..	..	?	None

† At about the time of conception.

to 1 million per ml., most of which were motile (table IV). The wife of the other patient (case 26), who had a sperm-count of only 4 million per ml., became pregnant three months after the implantation, but aborted in the third month of pregnancy.

Pregnancies

The wives of 11 (37%) of the 30 patients treated became pregnant during or soon after starting treatment, but one pregnancy ended in abortion. Table V shows the quality of the semen at the date nearest the time of conception, together with that of 2 patients whose wives became pregnant before treatment was started. The wife of 1 patient (case 17), who was treated with high doses of testosterone propionate, conceived two years and eight months after treatment was started. The sperm-count at this time is unknown, and conception is probably unrelated to the treatment. For this reason this case is not included. The same probably applies to case 13, where a second conception occurred two years and three months after the beginning of treatment.

Discussion

What has impressed us most in our observations is the pregnancy of the wives of husbands whose sperm-count was far below the recognised fertility level. We originally took as our lowest normal level Davidson's figure of 40 million spermatozoa per ml., but since then MacLeod and Gold (1951, 1953) have reported that a count of 20 million per ml. with a good motility index may be accepted as within the normal range. However, in this investigation 9 patients, 2 of whom had no treatment, demonstrated their fertility with sperm-counts ranging from nil to 10 million per ml. These findings have made us doubt the efficacy of treatment in most patients. There was little or no improvement in the quality of the semen as a result of androgen therapy, as may have been foretold from the statements in the introduction to this paper. Harvey and Jackson (1957), having shown only slight improvement in the semen after methyltestosterone therapy, suggested that the beneficial effect of testosterone is probably due to improved functioning of the epididymis and vas and to more efficient ejaculation, and not to any fundamental improvement in spermatogenesis. Although the number of patients is small, our observations show that the most effective form of therapy we have tried is the administration of testosterone propionate in high dosage for about three months. This was followed by pregnancies in 46%, although in 4 patients the sperm-counts were 10 million, 7 million, 4 million, and less than 1 million per ml.

Summary

30 patients with defective spermatogenesis were treated with preparations of testosterone—namely, methyltestosterone sublingually, testosterone propionate in high intramuscular dosage for three months, testosterone isobutyrate by intramuscular injection, or testosterone implants. In most cases there was little change in the quality of the semen. The wives of 11 patients became pregnant; the incidence of pregnancy was greatest when husbands were treated with high doses of testosterone propionate for three months (6 out of 13 cases). The sperm-counts of 7 fertile patients ranged from less than 1 million per ml. to 10 million per ml. Of 2 untreated patients who were fertile, one had azoospermia and the other had a sperm-count of 7 million per ml.

We are indebted to Ciba Laboratories Ltd. for supplies of testosterone isobutyrate ('Perandren M Crystules').

References at foot of next column

ANTAGONISM BETWEEN THE EFFECT OF ALDOSTERONE AND A SYNTHETIC STEROID LACTONE ON THE RENAL EXCRETION OF SODIUM AND POTASSIUM IN MAN

E. J. Ross
M.D., Ph.D. Lond. M.R.C.P.

J. E. Bethune *
M.D. Dalhousie, F.R.C.P.(C).

From the Medical Unit, University College Hospital Medical School, London, W.C.1

Antagonists to the action of aldosterone on the renal tubule are of potential clinical importance and have been sought for many years. Recently two synthetic steroid lactones, 3-(3-oxo-17β-hydroxy-4-androsten-17α-yl)-propionic acid γ-lactone (SC-5233), and its 19 nor-analogue (SC-8109), have been reported to possess this property when given to adrenalectomised rats (Kagawa et al. 1957) and to patients with hyperaldosteronism (Salassa et al. 1958). The purpose of the investigations

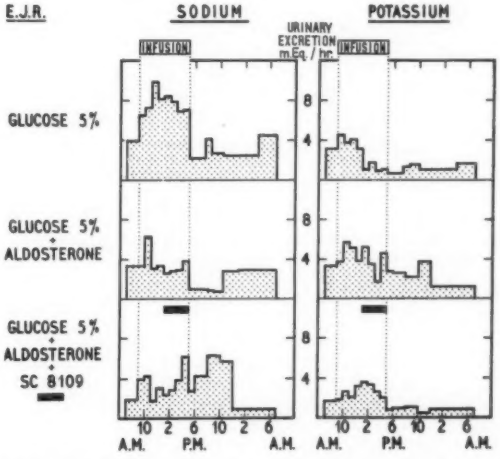

Fig. 1—Excretion of sodium and potassium during the control and experimental periods in E. J. R.

reported here was to demonstrate the capacity of the 19-nor analogue (SC-8109), given intravenously, to modify the effect of an intravenous infusion of aldosterone on the renal excretion of sodium and potassium in man.

Methods

Two normal subjects (the authors) were given 2-hourly feeds from 8 A.M. to 10 P.M. Each feeding consisted of 3 cream crackers, butter, 30 g. cheese, and 200 ml. orange squash, and contained 12 mEq. of sodium and 2 mEq. of potassium. The bladder was emptied completely at 6 A.M. and 8 A.M., then

* Present address: Department of Medicine, Dalhousie University, Halifax, Nova Scotia.

DR. SPENCE, DR. MEDVEI : REFERENCES

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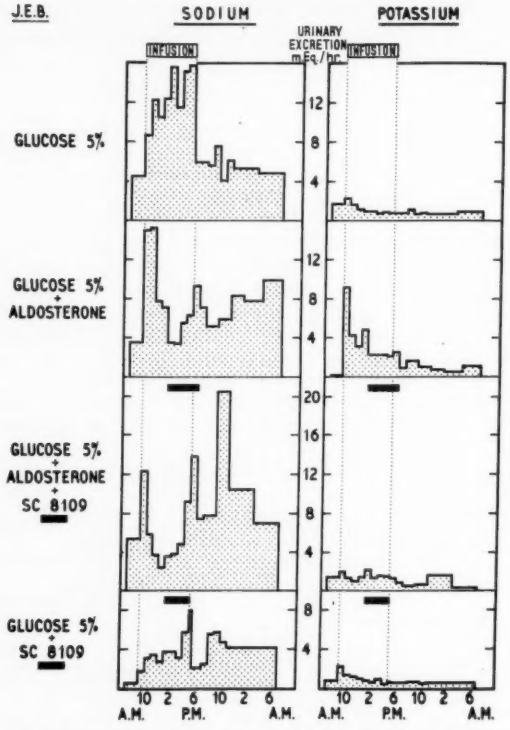

Fig. 2—Excretion of sodium and potassium during the control and experimental periods in J. E. B.

hourly until 6 P.M., and then at intervals until 6 A.M. the following day.

A control infusion of 800 ml. of 5% glucose in water was given over an 8-hour period to each subject, commencing at 8 A.M. in J. E. B. and at 9 A.M. in E. J. R. An amount of ethanol (18·5 ml.) equivalent to that used in the experimental studies was added at the 4th hour. On another day, 1 mg. of DL-aldosterone monoacetate was infused intravenously in 800 ml. of 5% glucose in water at the same times as above. After an interval of several days, 1 mg. of DL-aldosterone monoacetate was again infused. Compound SC-8109 was dissolved in absolute ethanol and forcibly ejected through a fine needle into the glucose solution containing the aldosterone at the 4th hour of the aldosterone infusion in E. J. R., and at the 5th hour in J. E. B. SC-8109 was infused at a rate of 55 mg. per hr. for 4 hours in J. E. B., and at a rate of 50 mg. per hr. for 4 hours in E. J. R. The addition of compound SC-8109 to the aldosterone solution resulted in a slight opalescence.

Blood was withdrawn for determination of serum-sodium and serum-potassium concentrations at zero, 4, and 8 hours after the start of the infusion.

Sodium and potassium concentrations in blood and urine were determined by flame photometry.

Results

The effect of the infusions on the renal excretion of sodium and potassium is shown in figs. 1 and 2.

The infusion of aldosterone resulted in a decreased excretion of sodium in both subjects, with no appreciable alteration in potassium excretion. The addition of SC-8109 during the second half of the infusion resulted in a reversal of the sodium retention caused by aldosterone. The infusion of SC-8109 alone to subject J. E. B. failed to cause significant sodium excretion.

There was a delay of 2 hours before an effect of the infusion of aldosterone on sodium excretion was apparent in J. E. B.; no definite conclusion on this point can be made in E. J. R. The duration of action of aldosterone in E. J. R. was much longer than in J. E. B. The addition of SC-8109 had no apparent effect until 3–7 hours after the infusion began; a prolonged sodium diuresis lasting for about 6 hours then followed.

No significant effect of SC-8109 on potassium excretion was demonstrated. Serum-sodium and serum-potassium levels were not significantly altered.

The influence of compound SC-8109 on the sodium retention consequent upon the infusion of aldosterone is more clearly seen when urinary sodium/potassium ratios are compared. In subject E. J. R. (fig. 3) the infusion of aldosterone resulted in a depression of the ratio to very low values which persisted until the last urine collection period. The addition of SC-8109 altered this ratio towards the value seen during the infusion of glucose alone, with a high peak 11 hours after the commencement of the infusion. In subject J. E. B. (fig. 4) the same alterations in ratio were observed but, because of the shorter duration of aldosterone action, were less pronounced. The time relationships of the peaks of the Na/K ratio were identical during the infusions of glucose and of compound SC-8109 in glucose.

Discussion

These observations directly confirm that this synthetic steroid lactone modifies the action of aldosterone on the renal tubular handling of sodium when given in amounts about 1000 times as great as the effective amount of DL-aldosterone infused. The antagonism is not immediate, but begins 2 hours and is greatest 8 hours after the start of the infusion, persisting for about 6 hours after the infusion has stopped. At this time, however, the effect of the aldosterone is disappearing so that it is difficult to estimate accurately the duration of the antagonism of SC–8109.

The infusion of SC–8109 alone to J. E. B. produced no change in the pattern of sodium excretion. This confirms the observations of Liddle (1957) and lends support to the

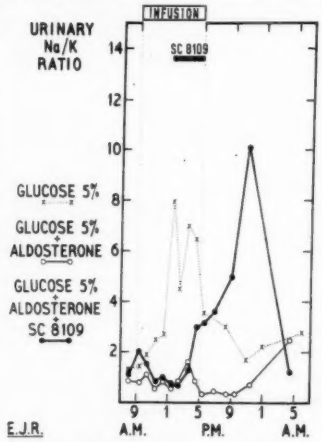

Fig. 3—Urinary sodium / potassium ratio during control and experimental periods in E. J. R.

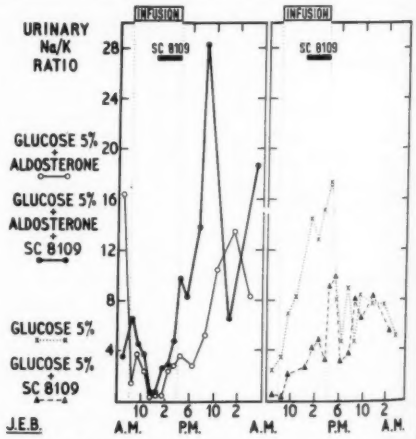

Fig. 4—Urinary sodium / potassium ratio during control and experimental periods in J. E. B.

thesis that aldosterone plays an insignificant role in the control of sodium excretion in normal subjects on a normal sodium intake (Ross 1958).

The fact that SC–5233 produced no alteration in sodium and potassium excretion in normal subjects on a high-sodium diet and in patients with Addison's disease maintained on salt alone, but does have an effect on sodium excretion in patients with Addison's disease treated with deoxycorticosterone acetate (Liddle 1957), suggests that these compounds do not have an independent direct action on the renal tubule but exert their activity only in the presence of sodium-retaining steroids. The mechanism of the block is not known, but the similar configuration of the molecules of aldosterone and the steroid lactone suggests that it acts by competitive inhibition.

A substance with the property of antagonising the action of aldosterone should be of great practical value as a tool in the investigation of the role of aldosterone in human homœostasis and possibly in the clinical management of excessive secretion of aldosterone. For this purpose it is preferable to amphenone B and 2,2-bis (parachlorophenyl)-1,1-dichloroethane (D.D.D.), substances which inhibit the synthesis not only of aldosterone but also of other adrenal steroids and have the disadvantage of causing unpleasant side-effects. No subjective symptoms of the infusion of SC–8109 were noted in our experiments, but it has been reported to cause drowsiness. SC–5233 has been administered to patients with congestive failure and the nephrotic syndrome in doses of 150 mg. every 3 hours intramuscularly, with a resultant modest sodium diuresis (Liddle 1957). The large amount of currently available spirolactone required to antagonise the effect of aldosterone is a disadvantage to their clinical use, but doubtless derivatives with a more favourable therapeutic ratio can be synthesised.

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THE HYPOTENSIVE EFFECT OF CHLOROTHIAZIDE

R. HALL
M.B., B.Sc. Durh.
MEDICAL REGISTRAR

S. G. OWEN
M.D. Durh., M.R.C.P.
RESEARCH ASSISTANT

From the Department of Medicine, University of Durham, and the Royal Victoria Infirmary, Newcastle upon Tyne

CHLOROTHIAZIDE was synthesised by Novello and Sprague (1957) and is chemically designated 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide. It has a powerful diuretic action, promoting excretion of sodium and chloride in equimolar amounts (Beyer 1958).

It is now generally accepted as potentiating the effect of ganglion-blocking agents used in the treatment of hypertension (Tapia et al. 1957, Heider et al. 1958, and others). Reports on the effect of chlorothiazide alone on high blood-pressure have varied. A significant fall was observed by Freis et al. (1958) and Wilkins et al. (1958), but Heider et al. (1958) did not confirm this hypotensive action. Freis et al. (1958) found that it had no effect on a normal blood-pressure.

We report here the effect of chlorothiazide on the blood-pressure of patients with arterial hypertension.

The Investigation

Thirteen patients with hypertension—none showing retinal changes more advanced than grade II (Wagener and Keith 1939)—cooperated in the study. They attended hospital fortnightly, when they were interviewed and their blood-pressure was taken in the sitting position. The trial lasted 6 months and consisted of three 2-month phases. No hypotensive treatment was given in the first 2 months, which constituted a control period. The patients were then divided at random into two groups, one of which received chlorothiazide tablets (0·5 g. twice daily) while the other had dummy tablets of identical appearance. For the final period the groups were transposed: those who had previously had chlorothiazide were given dummy tablets, and vice versa.

The patients were unaware that dummy tablets were being used for part of the study, and the investigators did not know which tablets a patient was taking at any particular time. But this double-blind arrangement was only partly preserved, since several patients complained of muscular weakness and polyuria, which suggested they were taking chlorothiazide. In patients with weakness the serum-potassium was estimated and potassium chloride was given by mouth.

The trial thus included two control periods. In the first of these, the patients knew they were receiving no treatment, but in the other they thought they were taking an active drug.

No restriction was placed on sodium intake, the patients continuing with their normal diet.

The results are shown in the table.

FORTNIGHTLY BLOOD-PRESSURE READINGS (SYSTOLIC/DIASTOLIC, MM. HG)

Case	Sex	Age	Control period				Dummy tablets					Chlorothiazide tablets				
1	M	79	170/100	180/110	200/100	190/110	180/110	170/90	170/100	150/90	170/90	160/90	150/90	140/90	150/90
*2	F	48	200/110	170/100	..	210/110	190/110	..	210/110	..	180/100	190/100	200/110	160/100	170/100
*3	F	62	190/100	190/120	230/130	240/150	220/130	240/130	220/110	200/120	220/130	210/130	160/100	190/120	160/100
4	M	71	250/120	250/120	210/110	210/120	230/120	250/110	200/110	190/120	210/110	210/110	220/110	230/120	230/120
*5	M	59	220/120	..	210/130	200/130	210/130	..	..	220/140	220/130	190/120	170/120	170/120	180/120
*6	F	52	170/90	170/100	170/100	170/100	150/90	150/90	130/80	150/90	150/100	160/90	140/80	130/80	160/90
*7	F	69	..	..	200/100	210/110	230/120	230/120	240/120	..	220/120	200/110	210/110	..	..
*8	M	46	..	220/130	200/130	210/130	210/130	210/120	220/130	200/120	210/130	220/120	200/120	180/120	170/110
*9	M	79	220/110	190/90	..	200/100	Discontinued [1]					150/90	130/80	160/80	120/70
10	F	66	260/150	250/150	250/140	220/120	250/130	260/140	230/140	230/140	250/150	230/120	Discontinued [2]			
11	M	59	190/110	210/110	190/100	170/100	220/120	220/100	190/100	200/110	200/110	200/100	190/110	160/100	170/100
12	F	69	..	260/150†	260/150†	260/150†	260/160†	260/140†	260/150†	260/160†	260/160†	260/150†	260/150†	260/150†	260/150†
13	F	51	..	220/140	250/140	230/140	230/140	230/140	230/140	220/140	220/140	200/130	160/110	200/130	160/110
Mean values			208/112	205/120	211/121	205/121	211/124	218/118	204/117	196/123	205/123	193/112	175/108	172/110	167/105
			207/119				207/121					177/109‡				

* Chronological order of periods: (1) control, (2) chlorothiazide tablets, (3) dummy tablets.
† In case 12 all systolic readings *exceeded* 260.
‡ Statistically significant change from control and dummy tablet periods.
1. Because of hæmorrhage from peptic ulcer.
2. Because of nausea and vomiting related to hiatus hernia.

Discussion

Chlorothiazide had a slight but definite hypotensive action. There was no significant difference in the mean blood-pressure during administration of dummy tablets and during the control period (207/121 and 207/119 mm. Hg respectively), but there was a fall when chlorothiazide was given (to 177/109 mm. Hg). Analysis of variance indicates that this change, though small (−30/−11 mm. Hg), was statistically significant. Moreover, the results do not exclude the possibility that a longer period of chlorothiazide would have produced a greater decrease. The downward trend of the mean values during the 2 months when it was given suggests that it might in fact have done so.

Summary

Oral chlorothiazide, 0·5 g. twice daily for 2 months, produced a small but significant fall in the blood-pressure of thirteen patients with arterial hypertension of moderate degree.

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Preliminary Communication

THE DETECTION OF ANTIFOAM EMBOLI FOLLOWING PERFUSION WITH A HEART-LUNG MACHINE

In the treatment of many hundreds of patients the bubble-type oxygenator has been used successfully for maintaining an extracorporeal circulation.[1 2] Difficulties, however, have been experienced by some workers, including ourselves, with this apparatus. After dogs have been perfused with this type of heart-lung machine, numerous small lesions are found in the brain. These have the pattern of embolic foci,[3] but no emboli have been demonstrated [3 4] and their nature is poorly understood.

In this communication we report the histological findings in tissues from seventeen dogs that were maintained for periods of up to 30 minutes on a DeWall-pattern bubble-oxygenator.[5] The defoamant used was polymethylsiloxane, applied as a fine spray to a piece of nylon gauze. Intravascular emboli were found in all the dogs. Those which survived the experiments long enough for histological changes to develop showed multiple cerebral infarcts, whether or not there had been clinical evidence of neurological damage.

The emboli consist of translucent globules of a substance which, like polymethylsiloxane, does not readily take up histological stains. Polymethylsiloxane is soluble in many organic solvents, and therefore much of it is removed during the preparation of tissues for paraffin embedding and mounting of sections in resins. Frozen sections mounted in a watery medium retain the emboli, which are seen more easily with a phase-contrast microscope. In size the emboli range up to 50 μ with an occasional one of 80 μ. Small ones (10–15 μ) were often seen in capillaries not particularly near areas of structural tissue damage. Larger ones (30–50 μ) were always close to infarcts. Many infarcts seem to have resulted from coincidental occlusion of several adjacent arterioles. No reactive cellular changes to the emboli have been observed even after 3 weeks.

In the brain the infarcts and areas of lesser ischæmic damage were usually less than 3 mm. in diameter. The smaller ones were almost confined to the white matter, the larger ones involved grey and white matter. This is in agreement with experimental observations [6] that small emboli of paraffin wax (less than 15 μ), though found in large numbers in the cerebral grey matter, do not (because of the considerable capillary net) produce infarcts there but only in the white matter.

Other forms of emboli have been sought without success apart from one small fibrin embolus. Microbubbles of oxygen disappear within 48 hours [7] and would not be visible in the greater part of our material. We think that nearly all the infarcts we observed are due to antifoam, since emboli of this substance were discovered in those lesions examined by serial sections after no clear cause was found in the initial slide.

Antifoam particles are much more easily detected in the kidney, where the glomerular tufts provide effective filters, than in the brain. They were present in all of the dogs' kidneys examined. In the least affected animals 25% of the glomeruli were involved.

Polymethylsiloxane is a grease-like substance which, when applied to a surface, does not form a uniform film unless special precautions are taken. Globules measuring up to 80 μ can be seen on the surface of the apparatus. Fortunately the substance is an extremely effective defoamant and can be used in very small quantities, especially if other precautions are taken to minimise foaming in the apparatus. It can be baked on to the wall of the defoaming chamber by autoclaving.[8]

Although we report unequivocal brain damage due to antifoam emboli, we do not intend in any way to condemn the DeWall bubble-oxygenator. The purpose of this communication is to draw attention to the problem of defoamant embolism. In addition we would stress that dogs may survive extracorporeal perfusion, without demonstrable neurological signs, and yet have extensive histological evidence of brain damage.

We wish to acknowledge research grants from the board of governors, United Manchester Hospitals, and the Manchester Regional Hospital Board.

P. O. Yates
M.D. Manc.
A. B. Cassie
M.B. Edin., F.R.C.S.
J. F. Dark
M.B., B.SC. Manc., F.R.C.S.
G. D. Jack
M.B. Edin., F.R.C.S.E.
A. G. Riddell
M.S. Lond., F.R.C.S.

Departments of Surgery and Pathology, University of Manchester

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New Inventions

AUTOMATIC DIATHERMY SWITCH AND SELF-CLEANING PROBE

THE surgical diathermy apparatus commonly used in hospitals has several disadvantages. First is the very real danger of a diathermy burn after accidental depression of the foot-switch, either by human agency or as the result of the switch becoming wedged beneath the operating-table. Second, the foot-switch frequently becomes displaced during operations, and the surgeon, often at a crucial point, has to take his eyes away from the wound to locate it. Lastly, when used for cutting, the diathermy needle becomes coated with carbon and loses its efficiency.

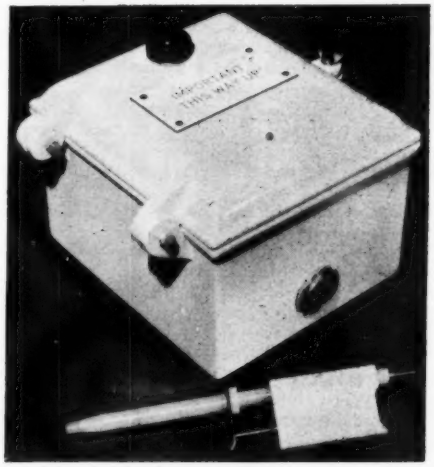


Fig. 1—Above: the electronic switch mounted in its airtight box. On its near side is the socket for the flash-proof plug and multi-core cable that connects it to the diathermy apparatus. Below is the self-cleaning probe whose needle is exposed for use by pulling the pistol grip and so retracting the spring-loaded barrel and its contained needle-scraper.

The apparatus here described overcomes all these disadvantages. The need for a foot-switch and hence the danger of accidental burns is eliminated by an electronic control contained in a small airtight box connected by cable and flash-proof plug to the diathermy apparatus (fig. 1). This device detects the minute change in electrical potential when the probe touches the patient, and responds by switching on the diathermy machine and at the same time giving, by means of a buzzer, audible warning of its actuation. Used with this automatic switch is a specially insulated self-cleaning probe. In this instrument the tungsten needle is shielded by a spring-loaded sheath; and the needle is exposed for use only when this sheath is retracted by pressure on the pistol grip. A scraper is contained in the sheath, and this cleans the needle each time the pistol grip is released. The probe can be sterilised by boiling or autoclave, and is used with the normal diathermy lead.

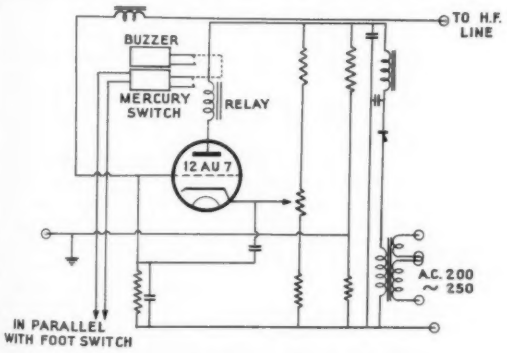


Fig. 2—Circuit diagram of the electronic switch.

The patient is in a circuit of such high impedance that he is exposed to no electrical danger.

Electronic Switch

The circuit consists essentially of a valve biased beyond cut-off with its grid connected through a filter to the live terminal of the diathermy machine and hence to the diathermy probe (figs. 2 and 3). Contact of the probe with the patient releases the bias on the valve, causing it to conduct and operate a relay that in turn switches on the diathermy machine. When the needle is removed from the wound the diathermy machine is switched off automatically by a reversal of this electrical process. With this arrangement there can be no danger to the patient because the maximum current that can pass is no more than a few micro-amperes.

Flash-proofing is effected by making the box containing the apparatus airtight and fitting the lid with a switch that renders the machine inoperative when it is open.

To ensure that the apparatus is switched on anew at the beginning of each operation, a self-holding relay is combined with the on/off switch. In this way the risk of burns as the result of accidental use of the automatic switch with an ordinary unguarded probe is eliminated. During an operation the surgeon may, by switching off the apparatus, revert immediately to foot control.

A further refinement is a "press-to-test" button with which the proper operation of the apparatus may be checked.

Self-cleaning Probe

The handle and sheath are made of polytetrafluoroethylene ('Fluon'), an inert, water-repellent and heat-resisting plastic material. For easy replacement the tungsten needle is held by a small chuck made, like all the other metal parts, from stainless steel. This probe may be used with advantage with the conventional foot control if an automatic switch is not available.

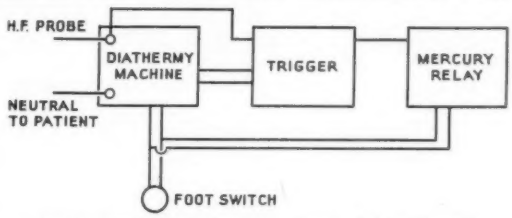


Fig. 3—Block schematic arrangement of the apparatus.

The electronic switch or "trigger" is mounted together with the mercury relay in the airtight box. The mercury relay is necessary because conventional contacts tend to burn out, particularly when used with the old spark-gap type diathermy machines of high impedance.

EVALUATION

This apparatus has proved satisfactory in use. It increases the safety and convenience of surgical diathermy and can be used with all existing diathermy machines, internal connection of a cable only being required.

The apparatus is manufactured by the Ellis Optical Company, Mayday Road, Thornton Heath, Surrey.

A. M. N. GARDNER
B.M. Oxon., F.R.C.S.
Torbay Hospital, South Devon.

C. J. T. ARCHER
M.B. Manc., D.A.
General Hospital, Northampton.

A. LEEMANS
Central Glass Blowing Department, University of Oxford.

Reviews of Books

Behaviour and Physique

An Introduction to Practical and Applied Somatometry. R. W. PARNELL, M.A., D.M., M.R.C.P., research physician, Warneford Hospital, Oxford. London: Edward Arnold. 1958. Pp. 134. 28*s*.

THE study of the relation of body types to disease has a history stretching back to Hippocrates. It has received renewed impetus in recent years from the work of Kretschmer in Germany and Sheldon in America. Dr. Parnell has been pursuing research in this subject for several years at Oxford, and this book is largely a record of his own work. He has followed Sheldon's method of assessment of body build from standard photographs, and also a related method of his own based on direct measurements. His categories depend essentially on the relative amount of fat and of muscle and bone in the body, and on the linearity of the skeleton. Thus an Mf individual is one who is muscular, moderately fat, and stocky in build, an Lm is one who is linear in build, moderately muscular, and carries little fat. Among stocky individuals there are Mf and Fm types, among individuals of average build Ml and Fl types, and among individuals of linear build Lm and Lf types.

The applications this book describes of somatometry to education and mental health are convincing. Muscular boys do badly in the grammar-schools entrance examination, probably not because they are unintelligent, but because their interests are not academic. At the university in England boys who are really muscular are rare. At the university, too, the relatively muscular students take up practical subjects, such as medicine, dentistry, and engineering, while the linear individuals are the theorists, mathematicians, lawyers, and art students. Lf individuals, if they are going to become mentally ill, do so early in life; in contrast, Ml individuals seldom break down till middle age, while Mf individuals are resistant to mental breakdown. Again, if Mf or Ml individuals develop thought disorder they are likely to develop the paranoid form, and their stay in hospital will be relatively brief. The applications of somatometry to choice of marriage partner and fertility are based on smaller numbers, but are suggestive. On genetic grounds one might expect the central types to be the most fertile, and this seems to be the case. More surprising is the way that the sex-ratio of the children appears to vary with the body build of the parents.

Dr. Parnell's book makes it clear that the subject is a fascinating one, and well worth further investigation. There is, however, obvious room for improvement in the methods used, and there is need for a better theoretical basis for these studies. The height/weight ratio, for example, is a crude way of measuring linearity and, as Parnell notes, it will fluctuate with age and nutritional state. Further, the genetics of body build urgently need investigation, so that it may be seen whether the associations with temperament and health are related to genotype or phenotype.

Parasitic Animals

2nd ed. GEOFFREY LAPAGE, M.A., M.D., M.SC. Cambridge: Heffer. 1958. Pp. 355. 25*s*.

FOR the medical profession the curse of parasitology is its intrinsic interest. Its history is romantic: were not ova of *Schistosoma hæmatobium* found in a mummy of the twentieth dynasty? Its life-cycles are intellectually satisfying in their circular completeness: there are no loose ends and yet problems enough for the most ambitious student. Average technical competence will produce elegant microscopic preparations of surpassing beauty (of which there are many in this book). The result is that far too many parasitologists seem to look on the host as a backcloth against which their darlings perform intricate evolutions, whereas to the doctor these worms and protozoa are no more than special instances in the corpus of general pathology. Dr. Lapage has written a book which must be approved by both parties. It is in the main a collection of apt examples to illustrate the well-ordered complexity of the relations between the mammals and some of the lower orders of life which depend on them. There is enough of the biology of the parasites and of the reactions of their hosts to make a convincing story. If he propounds some general principles of parasitism these are often enough principles-with-exceptions and the more interesting for that.

This book will not enable the medical student to distinguish between ancylostoma and necator (and a good thing too), but he can learn that hookworm disease is a biological phenomenon the effects of which upon man can be diminished by rational measures. The pathology of malaria depends upon the reproductive cycle of the parasite in man: the epidemiology upon the diverse habits and distribution of many species of anopheles. Yet the two are linked and the effect on man depends upon their sum. Because in this country it is the veterinary surgeon rather than the doctor who is most concerned with parasitic diseases it is proper that many of the examples should be taken from domestic animals. We laymen dose our dogs and horses "for worms" but we do little to prevent infestation.

This book is suitable for anyone who takes pleasure in good sense and good writing. It would be an excellent prize for the 6th-form scientist and a stimulating tonic for the weary physician. Pictures and binding are excellent.

Transportation of the Injured

CARL B. YOUNG, JR., M.P.H. With the collaboration of CARL B. YOUNG, M.D., F.A.C.S. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 238. 51*s*.

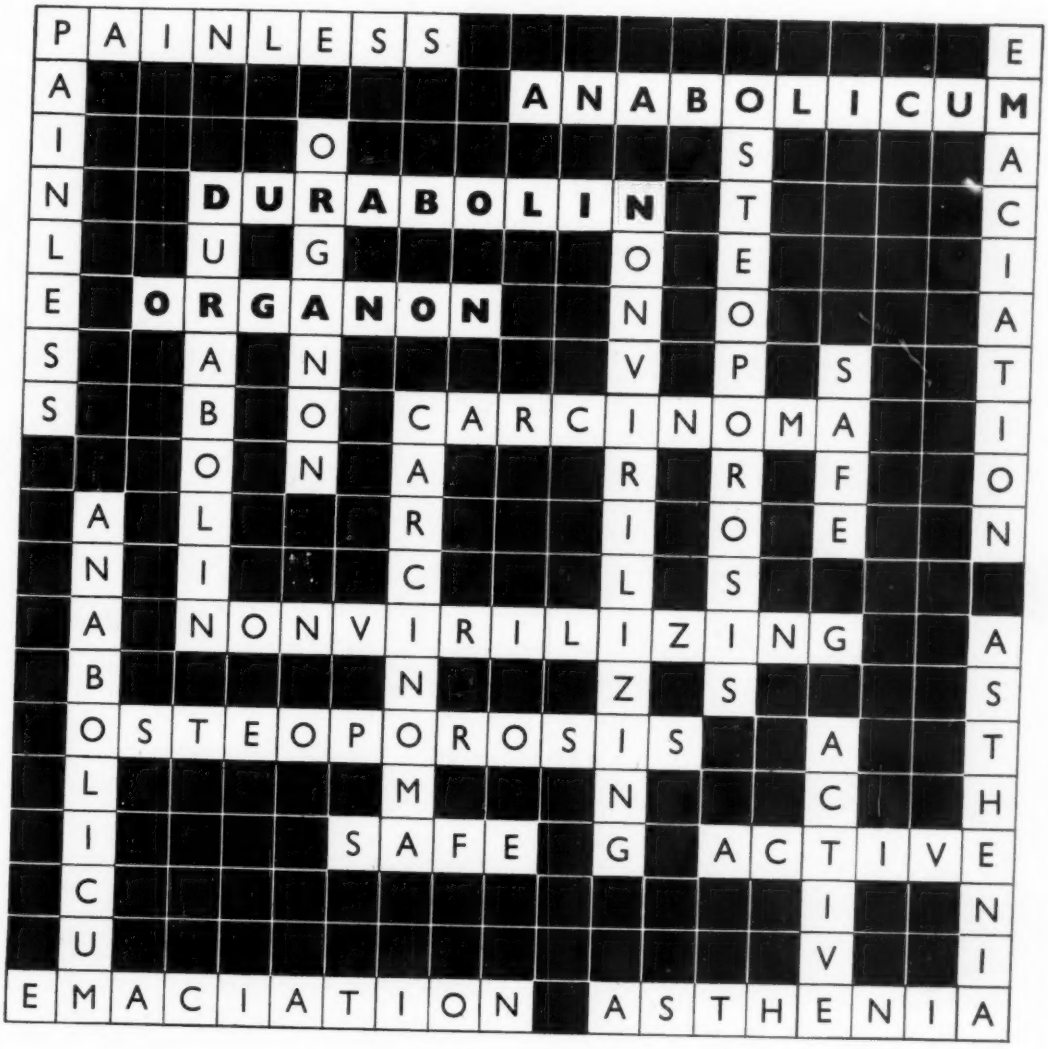
THIS excellent book has a much wider scope than its title suggests. Though the main emphasis is on trauma, the most important medical and obstetrical emergencies are also covered, and the first 150 pages, written primarily for the instruction of ambulance personnel, give details of first-aid care for these conditions. The remainder deals with the organisation of an efficient ambulance service and discusses the relative responsibilities of local medical societies, hospitals, and local authorities in this matter. There are many good photographs and diagrams.

The standard of the emergency and resuscitation measures and their presentation are, in general, very high. The description of procedures for coping with respiratory obstruction and arrest are outstanding and their importance is repeatedly and rightly stressed. The amount of theory is restricted to what is needed for a clear understanding of practical work. There is some sensible advice on how to deal with incidents which may later involve police action. On the administrative side, it may be argued that the suggestions for basic ambulance equipment are too lavish and expensive for anywhere except America, but local authorities would do well to aim at a high standard. The importance of really skilled emergency care is not always appreciated by those who have to decide how much to spend.

Clinical Enzymology

Editor: G. J. MARTIN, SC.D., research director, National Drug Co., Philadelphia. London: J. & A. Churchill. 1958. Pp. 230. 42*s*.

THIS rather curious medley of material begins with an essay by the editor which surveys engagingly the broad aspects of protein biology and develops a number of intriguing biological parallels with physical ideas, such as the exclusion principle in atomic structure and relativity. The concluding chapter is also by Dr. Martin and gives a challenging apologia for the therapeutic administration of enzyme preparations. The rest of the book contains accounts of the structural and physical chemistry of enzymes and of the diagnostic use of enzyme determinations. These topics, especially the last, are somewhat cursorily treated, and in the chemical sections the selection of particular enzymes for discussion, on the arbitrary basis of their claims to clinical usefulness, militates against a satisfactory systematic approach. In the clinical section much information is catalogued rather than appraised, and trypsin in particular seems to command a disproportionate amount of attention. There is much interesting reading in some parts of the book, but others may prove disappointing to both clinician and enzymologist.



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THE LANCET
LONDON 17 JANUARY 1959

Is Peptic Ulcer an Endocrine Disease?

THE gastrointestinal mucosa is second only to the skin in proneness to minor injury; and it would be remarkable if we lived through a single day of our lives without abrading, eroding, bruising, or scratching it—inflicting on it, in pathological parlance, acute ulcers. The real mystery begins when a tiny proportion of these lesions, almost all situated over a relatively short segment of foregut, fail to heal without symptoms. Clinically this troublesome minority falls into two groups. In the first are those initially minute breaches of the mucosa which develop into large, indurated, chronic ulcers—much as trivial abrasions on the unhealthy skin can be the starting-points of intractable varicose ulceration. The second group consists of acute erosions which pursue a brief but extremely aggressive course: they bleed, they perforate, they may kill. Despite a good deal of inspired guesswork, the reason for either of these atypical courses remains unknown. It seems that in the first the processes of healing are continually trying to catch up with the processes of destruction but fail by a short head; and that in the second there is a more transient but more severe breakdown in the mucosal repair mechanism. It is not unreasonable to assume, moreover, that this can be due either to local or to general disease.

We have already commented on the occasional association of multiple gastrointestinal ulcers, non-insulin-secreting islet-cell adenomas, and massive hyperchlorhydria [1]: this syndrome, first described by ZOLLINGER and ELLISON, [2 3] is perhaps an extreme example of the fulminating form of acute ulceration. The simplest link between its chief manifestations could be a hormone, secreted by a group of pancreatic islet cells, which stimulated the gastric secretory cell-mass. The colossal outpouring of acid gastric juice could certainly account for the seemingly total breakdown of the normal mucosal defences in the stomach, the duodenum, and even the jejunum. There has, in fact, been a good deal of speculation about the identity of this hormone; and the first favourite—glucagon—is still in the running. Dr. SUMMERSKILL, whose carefully planned investigations we print on p. 120 of this issue, gives no categorical answer as to whether or not such a hormone actually exists; but he sheds light on many of the syndrome's hitherto unexplained features, such as the often severe and even fatal diarrhœa; and he gives proof of the scope for radical surgery. The full benefit that his patient derived from this treatment cannot yet be assessed, but the operation was undoubtedly life-saving at the time. Mr. PENDER's case (p. 123) also underlines the need for purposeful surgery; but, in addition, his patient's family history hints at another curious syndrome—that of multiple endocrine tumours—and its association with peptic ulcer. That the functional interdependence of members of the endocrine system may have an anatomical basis has been known as a postmortem-room curiosity for many years [4–7]; but that this can be clinically significant is only now being recognised.[8–11] Multiple endocrine tumours may apparently be not uncommon; and, since there is nothing to suggest that a tumour in one gland can induce tumours in others, WERMER [8] is probably right in regarding them as distinct but "coordinated" manifestations of a developmental anomaly.

It was long ago postulated that individual endocrine glands can play a part in the ætiology of peptic ulceration. Before the pancreatic alpha-cells won so much attention, the "ulcerogenic" properties of the parathyroid gland and of the adrenal hormones were extensively investigated; and it is now widely believed that hyperparathyroidism and peptic ulcer are definitely linked.[12–18] Even if one hesitates to term peptic ulcer (as do some American and Continental workers) a "common" manifestation of parathyroid hyperfunction, parathyroid adenomas or hyperplasia can undoubtedly present with peptic-ulcer symptoms—though all that is known with reasonable certainty about the nature of this association is that it has very little or nothing to do with abnormal calcium-phosphorus metabolism.

The effect of adrenocortical hypersecretion on the gastrointestinal mucosa may be more complex, but it is no less real. Apart from the occasional acute ulcer complicating Cushing's disease, a mixed bag of "stress" ulcers are rapidly gaining in clinical importance.[19 20] For over a century the fulminating, bleeding, acute ulcer—"Curling's ulcer"—has been a dreaded late complication of extensive burns; and it is now recognised as a member of a much larger group. This group includes such entities as "air-raid ulcer" and "hunger ulcer", as well as "septicæmia ulcer", "head-injury ulcer", and post-traumatic and postoperative acute ulcers. The last two could be further subdivided according to the type of the injury or operation; but subgroups would have in common the considerable severity of the trauma, or at least severity relative to the patient's age and general health. (With the increasing magnitude of operations and the better chance of immediate survival after injury, this complication takes an increasing toll of patients apparently on the road to recovery.) In the

1. *Lancet*, 1957, ii, 1151.
2. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
3. Ellison, E. H. *Surgery*, 1956, **40**, 147.
4. Lloyd, P. C. *Bull. Johns Hopk. Hosp.* 1929, **45**, 1.
5. Kalbfleisch, H. H. *Frankf. Z. Path.* 1937, **50**, 462.
6. Shelburne, S. A., McLaughlin, C. W. *J. clin. Endocrin.* 1945, **5**, 232.
7. Underdahl, L. O., Woolner, L. B., Black, B. M. *ibid.* 1953, **13**, 20.
8. Wermer, P. *Amer. J. Med.* 1954, **16**, 363.
9. Fisher, E. R., Flandreau, R. H. *Gastroenterology*, 1957, **32**, 1075.
10. Zollinger, R. M., McPherson, R. C. *Amer. J. Surg.* 1958, **95**, 359.
11. Case Records of the Massachusetts General Hospital. *New Engl. J. Med.* 1957, **256**, 1153.
12. Rogers, H. M., Keating, F. R., Jr., Morlock, C. G., Barker, N. W. *Arch. intern. Med.* 1947, **29**, 307.
13. Berlin, R. *Acta med. scand.* 1949, **135**, 18.
14. Elkeles, A. *Lancet*, 1953, i, 770.
15. St. Goar, W. T. *Ann. intern. Med.* 1957, **46**, 102.
16. Hellström, J. *Acta endocr., Kbh.* 1954, **16**, 30.
17. Läuchli, P. *Schweiz. med. Wschr.* 1950, **80**, 1332.
18. Kirsner, J. B. *Bull. N.Y. Acad. Med.* 1953, **29**, 477.
19. Bogardus, G. M., Gustafson, I. J. *Surgery*, 1956, **39**, 222.
20. Helsingen, N., Hillestad, L. *Ann. Surg.* 1956, **143**, 173.

group of peptic ulcers associated with adrenocortical dysfunction some workers would include those developing during corticoid therapy[21-23]; but we can hardly be too cautious in describing any treatment as " ulcerogenic ". If this term is used loosely (as it so often is), simply implying the presence of acute ulcers, then not only are most drugs bought at the chemist's ulcerogenic, but so also are most breakfast cereals. What we should be seeking is not so much " ulcerogenic " as " anti-ulcer-healing " agents; and whether cortisone is one of these is still debatable.[24]

Little imagination is required to see the Zollinger-Ellison syndrome as a particularly violent kind of peptic ulceration associated not specifically with pancreatic alpha-cell tumours or hyperplasia but with a more complex pattern of pluriglandular adenomatosis; nor is supporting evidence for this view entirely lacking.[7-11] Distant endocrine tumours (many of which are almost microscopic) can easily be missed when attention is riveted on the pancreatic islets—just as many islet-cell tumours may have been missed in the past. But too much speculation may frighten the clinician into dismissing the syndrome as an esoteric novelty. In its milder forms it may, in fact, be neither new nor rare; and it is certainly not without immediate clinical importance. Since success in treatment depends on timely recognition, ulcers which perforate two or three times, those which fail to respond to treatment, those which recur often or soon after treatment, and even those which do not accord with the usual pattern, should be suspected and investigated. And if, with the gradual breaking-down of barriers between syndromes, disease entities, and body systems, medicine seems to be becoming too difficult, it is surely also becoming more interesting.

Mitral Incompetence

IMPORTANT regurgitation at the mitral valve results most commonly from rheumatic infection, but it may also complicate congenital heart-disease or follow bacterial endocarditis or cardiac infarction. In rheumatic mitral incompetence the valve is usually extensively damaged, with shortening of the posterior valve leaflet and of the chordæ, fusion of the commissures, and often calcification. These lesions tend to produce a rigid stenosed valve which fails to close properly. Often valve substance is lost owing to retraction and shrinkage of the leaflets and chordæ and dilatation of the annulus fibrosus; and this type of disease usually leads to severe incompetence with less stenosis. Mitral incompetence tends to augment itself because associated enlargement of the left ventricle causes further stretching of the annulus so that a vicious circle is set up.[25 26] In congenital heart-disease incompetence may result from a cleft mitral valve in cases of partial or total persistent atrio-ventricular canal, and from anomalous insertion of the chordæ, which are unduly short, in cases of ventricular septal defect or corrected transposition of the great vessels.[25] In bacterial endocarditis destruction and loss of leaflet tissue from necrosis leads to incompetence; and in the subacute form the mitral valve is often already the seat of slight organic disease. Acute severe mitral incompetence may result from rupture of chordæ following myocardial infarction or, occasionally, from valvotomy for mitral stenosis.

The diagnosis of mitral incompetence presents no great difficulty; the main problems concern assessment of degree and surgical correction. Considerable lone or dominant mitral incompetence is less likely than tight stenosis to give rise to pulmonary œdema, hæmoptysis, and systemic embolism; but the ultimate outcome is less favourable, principally owing to the better results of surgical treatment of mitral stenosis. The clinical picture is well recognised: a small, jerky arterial pulse; hyperdynamic left ventricle; pansystolic murmur at the apex conducted to the axilla and waning on inspiration; and third heart sound and short apical mid-diastolic murmur. Pulmonary hypertension is not usually severe unless appreciable stenosis is also present; but atrial fibrillation and considerable or gross enlargement of the left atrium are common. Gross calcification of the mitral valve is common when stenosis and incompetence are combined, but is uncommon in lone severe incompetence. The cardiogram usually shows biventricular hypertrophy, and in some cases the left ventricle is abnormally dominant.

The hæmodynamic abnormalities in severe mitral insufficiency have been extensively studied by cardiac catheterisation.[27-29] The left atrial pulse shows a high peaked v wave, no c wave, and a rapid descent of the v wave (" y " descent). There is little or no pressure gradient across the mitral valve in diastole, and, in contrast to mitral stenosis, the mean left-atrial pressure is not greatly raised. The left-atrial pulse in pure mitral stenosis is strikingly different, having a high diastolic pressure gradient across the mitral valve and a slow y descent. When stenosis and incompetence are combined, however, the pulse form is not diagnostic. Calculation of the rate of descent of the v wave (y descent) from the formula of OWEN and WOOD (Ry/v) has proved helpful, a ratio of more than 1·5 usually denying appreciable obstruction.[30] The dye-dilution techniques for the detection and quantitation of mitral-valvular incompetence, introduced by SHILLINGFORD,[31] is of considerable value. Mitral incompetence shortens the appearance-time of dye particles reaching the ear oximeter when dye is injected into the pulmonary artery, and increases the spread of the curve. The degree of incompetence can be assessed by measuring the ratio of the appearance-time to the spread. A ratio of 3 or less indicates slight or absent regurgitant flow,

21. Gray, S. J., Ramsey, C. G., Thorn, G. W. *Ann. intern. Med.* 1956, **45**, 73.
22. Nabarro, J. D. N., Stewart, J. S., Walker, G. *Lancet*, 1955, ii, 993.
23. Davis, T. A., Zeller, M. *J. Amer. med. Ass.* 1952, **150**, 31.
24. Meltzer, L. B., Bockman, A. A., Kanenson, W., Cohen, A. *Gastroenterology*, 1958, **35**, 351.
25. Edwards, J. E., Burchell, H. B. *Proc. Mayo Clin.* 1958, **33**, 497.
26. Lillehei, C. W., Gott, V. L., deWall, R. A., Varco, R. L. *J. thorac. Surg.* 1958, **35**, 154.
27. Marshall, H. W., Wood, E. H. *Proc. Mayo Clin.* 1958, **33**, 517.
28. Marshall, H. W., Woodward, E., Jr., Wood, E. H. *Amer. J. Cardiol.* 1958, **2**, 24.
29. Ross, J., Jr., Braunwald, E., Morrow, A. G. *ibid.* p. 11.
30. Owen, S. G., Wood, P. *Brit. Heart J.* 1955, **17**, 41.
31. Shillingford, J. *ibid.* 1958, **20**, 229.

4–6 moderate regurgitation, and over 6 severe regurgitation. But dye-dilution curves will not exclude slight incompetence, and regurgitation cannot be measured in the presence of a very low cardiac output and very large left atrial volume. Assessment of the degree of incompetence in this way agrees well with the clinical assessment.[7] The degree of mitral incompetence can usually be deduced from combined clinical, radiographic, cardiographic, hæmodynamic, and dye-dilution methods. An important clinical, pathological, and hæmodynamic correlation has been recorded by McDONALD et al.[32]; and MARSHALL and WOOD [27] have indicated the value of left-atrial-pressure pulses, measurement of the mitral-valve gradient by left-heart catheterisation, and dye-dilution curves made from the pulmonary artery. Left-heart catheterisation should not be regarded as a routine procedure, but reserved for especially difficult problems.

With improved diagnostic methods it is encouraging to learn of new surgical approaches. GUIDRY et al.[33] report their experiences in 6 cases treated by an operation known as mitral annuloplasty, in which the annulus fibrosus is plicated under direct vision during total cardiopulmonary bypass. All the patients survived the operation and were improved, and hæmodynamic data obtained after the operation showed reduction in incompetence. LILLEHEI et al.[26] have reported a similar operation utilising pledgets of ' Ivalon ' to buttress the shrunken cusp when loss of valve substance is prominent. 5 cases were operated upon, 4 having a simple annuloplasty and 1 a combined annuloplasty and prosthesis; all were greatly improved. On the experimental side, ELLIS and BULBULIAN [34] have reported encouraging results with an artificial valve with an ivalon ring for fixation. If such a valve can be used in man a solution to the surgical treatment of extensively damaged and heavily calcified incompetent mitral valves may be in sight. Now that total cardiopulmonary bypass is a practicable routine procedure in this country,[35] the prospects for the effective treatment of severe mitral incompetence are bright. But physicians must play their part by referring patients to the surgeon before the disease has progressed to the stage of gross myocardial damage and persistent heart-failure.

To be Read a Second Time

WHEN Parliament reassembles next week the House of Commons' first task will be consideration of the Mental Health Bill published during the recess.[36]

The Bill is largely based on the recommendations of the Royal Commission on the Law relating to Mental Illness and Mental Deficiency, which reported in May, 1957.[37] That the Commission's proposals receive such substantial and speedy legislative translation is itself evidence both of the change in public opinion and of the administrative and therapeutic revival which has been taking place inside our mental hospitals. The feeling that physical and mental illness alike are forms of ill health, and that those who have to endure them are all patients, is winning ever wider acceptance. It is recognised that the mental patient should have free access to hospital treatment as he needs it, that his therapeutic course should not be unnecessarily beset by formalities and safeguards, that his segregation should not be unduly long or unduly strict, and that he should be offered reablement and convalescence within the community rather than in the hospital.

In practice this new responsibility of the community can be met only if the local authorities, on behalf of the community, provide suitable services for the patients. " General good will " and " acceptance in principle ", if they are to be really effective, must have the backing of such realities as more psychiatric social workers, more small residential homes, and more reablement centres. Many people have been uneasy because the need for this expansion of the local-authority services has coincided with the introduction of the block grant to local authorities. In announcing the details of this change [38] the Minister was careful to point out that allowance had been made for an expansion of the mental-health services. But, despite this Ministerial awareness of the difficulty, the new Bill is content to " empower " local authorities to provide services for mental defectives—to give local authorities " greater freedom " to organise services for the mentally ill. The Bill has already been criticised on the grounds of the inadequacy of mere permissiveness and the need for making the provision of these services obligatory. Some authorities will no doubt welcome the opportunity to extend and improve their work; but the incidence of services for old people suggests that under a permissive regime some areas, where there are perhaps local difficulties, will lag far behind. According to present arrangements, the block grant allows for expansion of these services at two and a half times the present annual rate. In a progressive area this may not be unreasonable, but to a laggard authority it will offer no encouragement to catch up.

The Bill has been widely and justly welcomed for its libertarian qualities, and it is perhaps ironic that another of its provisions which is causing anxiety arises from its avoidance of the use of compulsory powers. Under the new admission procedure hospitals will no longer be obliged to accept patients, and it is thought that this may sometimes make it difficult for a doctor to secure admission of an awkward and unsatisfactory patient. Some of these patients might well fall into the group which is to carry the much-discussed name of " psychopath ". The Bill accepts the Commission's use of this term (which was perhaps the least popular of their proposals), but has bravely included a definition, which the Commission deliberately omitted, and says that, in its own paragraphs at any rate, psychopathic

32. McDonald, L., Dealy, J. B., Jr., Rabinowitz, M., Dexter, L. *Medicine, Baltimore*, 1957, **30**, 237.
33. Guidry, L. D., Callahan, J. A., Marshall, H. W., Ellis, H. F., Jr. *Proc. Mayo Clin.* 1958, **33**, 523.
34. Ellis, H. F., Jr., Bulbulian, A. H. *ibid.* p. 532.
35. Cleland, W. P., Beard, A. J. W., Bentall, H. H., Bishop, M. B., Braimbridge, M. V., Bromley, L. L., Goodwin, J. F., Hollman, A., Kerr, W. F., Lloyd-Jones, E. B., Melrose, D. G., Telivuo, L. J. *Brit. med. J.* 1958, ii, 1370.
36. See *Lancet*, Jan. 10, 1959, p. 94.
37. See *ibid.* 1957, i, 1187.
38. See *ibid.* 1958, ii, 1221.

disorder means "a persistent disorder of personality (whether or not accompanied by subnormality of intelligence) which results in abnormally aggressive or seriously irresponsible conduct on the part of the patient, and requires or is susceptible to medical treatment". Nor does the Bill accept the recommendation that the feebleminded should be included in the "psychopathic group"—for which group it proposes to retain the use of the term "subnormality". In a letter this week Dr. HEATON-WARD discusses difficulties which he fears may arise from the proposals for the automatic discharge of many of these patients when they reach the age of 25.

One of the chief features of the Bill, and perhaps its legal raison-d'être, is the dissolution of the Board of Control and the substitution of the administrative novelty of mental-health review tribunals. Since there is to be a tribunal in each hospital region, these tribunals will have a local as opposed to a national character. To some patients the new bodies may seem less assuredly neutral and independent than the old; to others they may seem less aloof, more comprehensible, something belonging to "us" rather than to "them".

Other questions as well as, or instead of, these will no doubt be discussed at the second reading on Jan. 20 and will provide valuable material for Ministerial consideration before the Bill is sent to committee. A measure which is full of unfamiliar detail and which is so important to the welfare of so many people will be assured of the careful and sympathetic scrutiny of both Houses.

Annotations

TRACHEOTOMY TODAY

TRACHEOTOMY used to be performed mostly for diphtheria, and with the virtual disappearance of diphtheria it might have been expected to become a rare operation. That this has not happened was emphasised by a meeting on Jan. 7 of the Section of Surgery of the Royal Society of Medicine. The speakers included ear, nose, and throat surgeons, general surgeons, a pædiatrician, an anæsthetist, a neurosurgeon, and physicians interested in tetanus and in chest disease—a list that indicates the wide application of the operation.

Broadly speaking, tracheotomy may be indicated either if the patient cannot keep his upper airway clear, or if his lungs are embarrassed by intrabronchial material, such as pus, which he cannot cough up, or if his respiratory muscles are weak. In the first category come patients with paralysis due, for instance, to poliomyelitis, polyneuritis, or myasthenia gravis; patients who are deeply unconscious, such as those with head injury or barbiturate poisoning; and those with mechanical interference with their upper airway due to injury or surgery. In many of these conditions artificial respiration may be necessary, and the tracheotomy then forms a convenient route by which intermittent positive-pressure respiration can be started whenever required. The second category includes patients who (though not suffering from a paralysing disease) owing to general weakness cannot cough sufficiently to clear their chest despite urgent need to do so. Many of these patients are children with tracheobronchitis or the elderly with chronic chest disease. The third category is more debatable. Many patients with paralysis of the respiratory muscles also cannot guard their upper airway safely, and they must have a tracheotomy. But the patients who have respiratory weakness with a normal upper airway can be treated in a tank respirator, and this is common practice in this country. If, however, the patient has to be transported over a long distance tracheotomy and intermittent positive-pressure respiration may be necessary, and it has not been shown that these patients suffer any disadvantage compared with their fellows in tank respirators.

The wide scope of tracheotomy nowadays has led to a search for simpler methods of performing the operation [1 2]; and these procedures, though devised primarily for emergencies, have been used for elective tracheotomies. Misfortunes have, however, been reported as a result,[3] and in normal circumstances standard surgical technique should probably always be followed. Ear, nose, and throat surgeons will continue to perform most tracheotomies; but it seems that every surgeon should be prepared to undertake the operation. The time has not yet come, however, when physicians can perform a tracheotomy as easily and safely as a lumbar puncture.

PATHOLOGY CELLULAR AND SUBCELLULAR

THE Association of Clinical Pathologists celebrated the centenary of Virchow's *Die Cellularpathologie* with a symposium in October, and published it with admirable promptitude in the November issue of the *Journal of Clinical Pathology*. The record presents a valuable conspectus of many facets of the still very lively subject of the pathology of the cell.

The classic subject of tissue-culture is examined in breadth by Honor Fell,[4] reviewing its history and achievements, and in depth by Pulvertaft,[5] describing in revealing detail a single investigation into the origin of platelets for megakaryocytes. Robert Cruickshank [6] tersely and informatively reviews the cytology of bacteria. The strictly practical subject of exfoliative cytology is discussed by Bamforth and Osborn,[7] who are especially good on the (very long) history of the method and on the evils of the divorce between cytological and histological tumour diagnosis. An immunological approach to cytology is described by Berenbaum,[8] who uses an autoradiographic method to estimate the antibody content of single cells.

The most recent advances in understanding of what goes on within the cell in health and disease—subcellular pathology it should be termed today, rather than the cellular pathology that has been our main preoccupation for the past hundred years—have come chiefly from three lines of investigation: electron microscopy, the biochemistry of isolated cell particles, and histochemistry. The two papers devoted to these subjects are the most stimulating of the symposium. Harman [9] attempts the enormous task of correlating the findings of electron microscopy and particle biochemistry in a wide range of disease processes; and, though the profusion of information makes for heavy reading, and specialists may question some of his conclusions, many will find it a revelation of the enormous recent advances in this field—advances which have

1. Sheldon, C. H., Pudenz, R. H., Freshwater, D. B., Crue, B. L. *J. Neurosurg.* 1955, **12**, 428.
2. Salvatore, J. E., Maloney, W. H. *J. Amer. med. Ass.* 1957, **165**, 2077.
3. Smith, V. M. *ibid.* p. 2074.
4. Fell, H. B. *J. clin. Path.* 1958, **11**, 489.
5. Pulvertaft, R. J. V. *ibid.* p. 535.
6. Cruickshank, R. *ibid.* p. 483.
7. Bamforth, J., Osborn, G. R. *ibid.* p. 473.
8. Berenbaum, M. C. *ibid.* p. 543.
9. Harman, J. W. *ibid.* p. 495.

so far had a quite inadequate impact on pathology and medicine in general.

The old view that cytoplasm consisted of an active matrix in which were embedded inactive granules, mostly of storage or secretory end-products, is now reversed: practically all the activities of cytoplasm that we can study prove to be localised in granules of one sort or another, mostly of three major types. The mitochondria show under the electron microscope a complex structure of double laminæ, and when isolated are found to contain all the enzymes of the Krebs tricycle and the related phosphorylation systems. The lysosomes have a simple granular structure, and contain most of the lytic enzymes. The microsomes consist of chains of small vesicles which contain most of the cells' ribonucleic acid and enzymes concerned in protein and steroid synthesis and in the detoxification conjugations. There emerges a very clear picture—even if possibly oversimplified—of the localisation of the three major types of activity in the cell: energy release in the mitochondria, synthesis in the microsomes, and breakdown in the lysosomes. Special functions of specialised cells can in their turn be related to additional enzyme systems on one or more of these basic particle types, or to the presence of specialised particles such as the siderosomes of liver.

Harman marshals a surprising number of instances in which the site of action of some pathological process can be deduced more or less precisely. Several bacterial toxins, for instance, act directly on mitochondria. Diphtheria toxin *may* be nothing more abstruse than the protein component of the bacillus's own cytochrome B, capable of diffusing into mitochondria, replacing the host's corresponding protein, and so blocking the energy-producing cycle. The activity of the lecithinase α-toxin of *Clostridium welchii* probably depends on its ability to disrupt the lipid elements in mitochondria, with the same final effect: lipid-soluble toxic materials such as carbon tetrachloride act in the same kind of way, though here (as with thioacetamide) part of the trouble is a flooding of the mitochondria with calcium as a result of damage to their limiting membrane. Several vitamin and hormone mechanisms seem also to act through mitochondria. That most nebulous of entities—cloudy swelling—is beginning to acquire a new and more exact meaning, for all its features are apparently the result of the loss to the cell of the mitochondrial energy source, and all the agents which cause it act by damaging the mitochondria or their contained enzymes.

Information about the pathological role of lysosomes (the most recently recognised of these bodies) is scanty, and information about microsomes is much less precise than is that of mitochondria. But the effect of vitamin B_{12} or folic acid on hæmoglobin synthesis can be localised to these bodies. The binding of azo-dyes to liver-cell protein that is so essential a phase in the production of liver cancer by these dyes appears to occur in the microsomes. The detoxification function of microsomes is involved in constitutional hyperbilirubinæmia (Gilbert's disease), for this appears to be due to a defect in the liver microsomes of the glycuronidating enzyme system that normally converts fat-soluble bilirubin to its soluble excretable glycuronidate.

Pearse [10], discussing enzyme histochemistry, fills in the picture. Despised for long by both biochemists and histologists, histochemistry is rapidly rising to a position as *the* essential reconciliation of the two classical approaches to understanding cytoplasm. A major factor in this has been the shift of emphasis from the histochemical recognition of definable chemical substances within cells to the study of the enzymes which make these substances. Pearse discusses especially the dehydrogenases, of which ten or more can now be localised by various refinements of the tetrazolium technique. Histochemistry has always had a major advantage over biochemistry in the recognition of patchy lesions: analysis of extracts and homogenates cannot identify changes which affect single cells in an otherwise normal organ, just as it cannot demonstrate differences (which must exist) between cells at different levels of the normal renal tubule. Pearse's demonstration of varying enzyme content of the macula densa in hypertension, and of variation in enzyme content between adjacent cells of homogeneous-looking tumours, is therefore not unexpected. He goes further, however, and demonstrates differences between single mitochondria. Methods combining enzyme localisation with osmotic challenge are clearly of extraordinary sensitivity in detecting the earliest stages of damage to individual particles. But Pearse regretfully points out that the 45 enzymes demonstrable histochemically still fall far short of the 700 known to biochemists, and it is noteworthy that all but a few very crude histochemical techniques are still tied to the light microscope.

Perhaps the main lesson of this symposium is the unwisdom of any technician's neglecting his neighbour's techniques. To solve the arch-problem of biology—the structure and function of cytoplasm—we shall need all the techniques we know and many not yet thought of. But we make remarkable progress. Perhaps it is ungrateful to wish that Sir Roy Cameron had contributed to the discussion a survey of the evolution of the idea of the cell in pathology, and bridged the gap between Virchow and these modern developments as probably only he could do. Possibly he was unwilling to retread ground he has covered so well already.[11] Whatever the reason, he has given us [12] instead a picture of Virchow's background, social rather than scientific, whose erudite felicity is ample compensation.

PROGESTERONE AND RECURRENT ABORTIONS

For some time progesterone has been widely used to treat recurrent abortion in women with no apparent pelvic abnormality. Some workers [13 14] have administered the hormone in all such cases, others [15] only to those with a low level of excretion of pregnanediol; and high success-rates have been reported by both. Swyer and Daley [14] pointed out that good results were obtained also in their control group, and Bevis [16] achieved results as good as any with minimal treatment amounting to strong psychological support. Javert [17] also emphasises the value of psychotherapy rather than hormones.

Nevertheless Rawlings and Krieger [18] have continued to study the possibility that progesterone deficiency may account, at least in some cases, for repeated abortion. These workers studied pregnanediol excretion curves from weekly twenty-four-hour specimens in pregnant women (some of whom have received ethisterone), and they claim that this has enabled them to pick out the

10. Pearse, A. G. E. *ibid.* p. 520.

11. Cameron, G. R. Pathology of the Cell. London, 1952. New Pathways in Cellular Pathology. London, 1956.
12. Cameron, G. R. *J. clin. Path.* 1958, **11**, 463.
13. Bishop, P. M. F., Richards, N. A. *Brit. med. J.* 1952, i, 244.
14. Swyer, G. I. M., Daley, D. *ibid.* 1953, i, 1073.
15. Alder, R. M., Krieger, V. I. *Med. J. Aust.* 1957, ii, 122.
16. Bevis, D. C. A. *Lancet*, 1951, ii, 209.
17. Javert, C. T. *Obstet. Gynec.* 1954, **3**, 420.
18. Rawlings, W. J., Krieger, V. I. *Med. J. Aust.* 1958, ii, 561.

progesterone-deficient cases. Yet snags remain. Progesterone metabolism is very incompletely understood. Only 10–40% is excreted as pregnanediol in the urine,[19] and every laboratory report emphasises the wide day-to-day variation in the level of urinary pregnanediol. Further Coyle et al.[20] regarded the methods of estimation then available as subject to uncontrollable error, though a later method [21] is claimed to give greater accuracy. Certainly single readings are of little value. Rawlings and Krieger [18] gave ethisterone in doses of 10–200 mg. daily when the excretion of pregnanediol fell below what they judged to be a critical level; but Roland and Veprovsky [21] believe that a sudden severe drop in level usually denotes death of the fœtus. Since progesterone given by injection is first stored in the body-fat and then slowly excreted,[19] treatment, if it is to be effective, must almost certainly be initiated before the urinary level of pregnanediol has fallen seriously. Some doubt as to the value of progesterone therapy remains, then; and, as estimation of pregnanediol is not easy and is costly if repeated frequently, the method recommended by Rawlings and Krieger is unlikely to be widely adopted.

A better understanding of the hormone control in such cases will surely come from estimation of the serum levels of the hormones concerned. The importance of a (normal) high level of chorionic gonadotrophin in early pregnancy has already been emphasised.[22] It has now become possible to assess progesterone and pregnanediol in the blood in late pregnancy,[23 24] and in time doubtless the difficulties of estimation in the early months will be overcome. From such work may come real advances in our understanding of recurrent abortion.

MANAGEMENT COMMITTEES

CONSIDERING that the number of committees in this country now seems to be somewhere round 4·76 per head of population, we know far too little about how they work and what kinds are best for what purposes. We are certainly right in preferring the committee system to authoritarian rule; but the Health Service is only one of many national organs whose efficiency is impaired by having too many committees with too many members. Sooner or later, something must be done to reduce this element in administration to the minimum that will serve its important purpose; and many will welcome a report, entitled Committees and Communication,[25] from the Institute of Hospital Administrators.

This report is limited in scope and mostly about hospital group management committees. It does not, for example, discuss Lord Taylor's impressive arguments [26] in favour of having regional boards with not more than 8 (suitably paid) members, nor the suggestion that, with smaller regions and active house committees, the management-committee tier could be entirely removed from the structure.[27] But it usefully summarises a good deal of information about management committees (derived from the Newcastle, South East Metropolitan, Liverpool, and especially Manchester regions) and also their advisory and consultative committees. It recognises that a small committee (say 12) is likely to be more effective than a large one (of 20 or more), but points to the advantages obtainable from wide representation on a large committee with subdivision of work among subcommittees. In the Manchester region the average number of committee members is 17, and, though there are no fewer than fifty-four different titles for standing subcommittees, " the number appointed by any single hospital management committee does not exceed eight and may be as low as three ". The report says that, subject to local circumstances, " the most convenient committee structure will include a finance and general purposes subcommittee, with possibly one or two other standing functional committees, the greater part of the day-to-day committee work concerning particular hospitals being handled by house committees ". Attention is drawn to the possible advantage of having more women on the committees, and a higher ratio of younger members, between the ages of 30 and 45: " the average age of committee members in the Manchester area is between 55 and 60 and of women members 50 to 55, except for mental hospitals and mental deficiency institutions when it is nearer 60 ".

" We agree with the Guillebaud Committee that the proportion of medical members should not be excessive, though—in our opinion—it is necessary to goodwill and understanding that at least one or two senior members of the professional staff who are trusted spokesmen of the staff should be included. An obvious nomination would be the elected chairman of the medical staff committee. We are of opinion, however, that such appointments to a management committee of senior medical staff should be restricted to those holding exclusively senior clinical appointments under contract with the regional board . . ."

In discussing regional-board representation at management-committee level, the report illustrates the benefits to be gained from having a regional-board member serving also on a management committee: he becomes an informal channel of communication. But in practice the proportion of regional boards (14 in England and Wales) to boards of governors and management committees (over 400) is such that this channel could not be generally provided without further increasing the already unwieldy membership of the regional boards. This is but one aspect of a wider question to which we have already alluded: are not the regions too big and the boards too remote?

Many of this report's recommendations on working procedures will be helpful to committee members and hospital administrators alike. We could wish that more attention had been paid to the frequency of committee meetings and to their content. Many people feel that too many meetings are held to discuss matters of detail—a practice which must discourage the more useful type of committee member and also the hospital officer, who needs to be given enough scope to do his proper work properly. If fewer and smaller committees held fewer and shorter meetings and concentrated on policy, the hospitals might benefit greatly. Similarly, in a part of the report dealing with communications between hospital authorities and hospital officers, valuable guidance is given on the methods and types of communication, but relatively little is said about the content of the communications that are continually passing up and down, particularly between management committees, regional boards, and the Ministry of Health. Much time and paper is spent on collecting, collating, and dispatching reports and returns of various descriptions, and the question whether each is really necessary should be asked more often and with more vigour.

19. Davis, M. E., Plotz, E. J. *Fert. Steril.* 1957, **8**, 603.
20. Coyle, M. G., Mitchell, F. L., Russell, C. S., Payne, E. C. G. *J. Obstet. Gynæc. Brit. Emp.* 1955, **62**, 291.
21. Roland, M., Veprovsky, E. *Lancet*, 1956, i, 911.
22. Davis, M. E. *Clin. Obstet. Gynec.* 1958, **1**, 219.
23. Deshpande, G. N., Sommerville, I. F. *Lancet*, 1958, ii, 1046.
24. Aitken, E. H., Preedy, J. R. K., Eton, B., Short, R. V. *ibid.* p. 1096.
25. Report of a Study and Research Committee. Obtainable from the institute, 75, Portland Place, London, W.1. 1958. Pp. 33. *2s. 6d.* (post free 3s.).
26. Taylor, S. *Lancet*, 1951, ii, 725.
27. *Lancet*, 1958, ii. 28.

Special Articles

EXPERIENCES WITH A DISPOSABLE PLASTIC TRANSFUSION-GIVING SET

W. J. JENKINS, M.D., B.Sc. Wales — DIRECTOR
B. STONE, M.B. Manc. — DEPUTY DIRECTOR
NORTH EAST METROPOLITAN BLOOD-TRANSFUSION CENTRE, BRENTWOOD

G. S. A. KNOWLES, M.B., B.Sc. Lond., F.F.A. R.C.S.
CONSULTANT ANÆSTHETIST, NORTH MIDDLESEX HOSPITAL, EDMONTON

G. H. TOVEY, M.D. Brist.
DIRECTOR, SOUTH WESTERN BLOOD-TRANSFUSION CENTRE, BRISTOL

R. A. SHARPE, M.B. Brist.
HOUSE-PHYSICIAN, SOUTHMEAD HOSPITAL, BRISTOL

WHEN a plastic transfusion set manufactured in Great Britain became available, a subcommittee of the Medical Research Council Blood Transfusion Committee was formed to test its performance and to compare the incidence of thrombophlebitis after prolonged transfusions through this set and through sets made of rubber tubing and glass. The subcommittee reported (Medical Research Council 1957) that when plastic sets were used the incidence of thrombophlebitis was about half what it was when red-rubber tubing was used. Because of this finding, and because the issue of plastic sets abolishes the need to recover, clean, reassemble, and sterilise used rubber sets, the Ministry of Health decided to supply plastic sets, of modified design, through regional transfusion centres. The North East Metropolitan region introduced them last April and the South Western region followed in July. At the time of writing some 50,000 sets have been used in some 300 hospitals in the two regions.

Because the conventional red-rubber and glass set has given faithful service since 1939 and is thoroughly familiar to all sections of hospital staffs, any innovation in design was expected to evoke some criticism. In describing our own experience with the plastic sets, we discuss comments by clinicians and pathologists and record experiments directed towards improving the design.

Description of the Set

The set is manufactured in Britain by Capon Heaton & Co. Ltd., to comply with a Ministry of Health specification based on the recommendations of the M.R.C. subcommittee. It is made almost entirely of polyvinyl chloride; but the piercing-needle assembly, the filter, and the adaptors are made of nylon.

Fig. 1 shows the set as removed from its carton: the tubing is seen coiled round a cardboard former to prevent kinking during storage. Fig. 2 shows the set laid out for identification of parts.

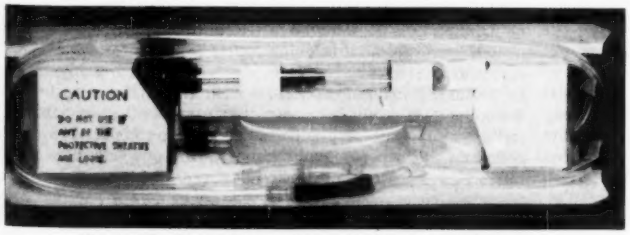

Fig. 1—The Capon Heaton disposable plastic recipient set.

The overall length from the tip of the piercing-needle to tip of the intravenous needle is 168 cm. (66 in.), making its effective length outside the bottle 162·3 cm. (63$^3/_4$ in.). The tubing has a minimum internal diameter of 4 mm. (The effective length of the glass-rubber set is 150 cm. [60 in.] and the internal diameter of the rubber tubing is 4·7 mm.) The piercing-needle, the air inlet, and the giving-needle adaptor are covered by plastic sheaths ensuring that the interior of the set remains sterile. The nylon piercing assembly incorporates a metal needle leading to the air-inlet tube. The latter is long enough to allow the distal end to be secured above the level of fluid in the bottle and terminates in an air filter and securing hook. The free end will take a male Luer adaptor.

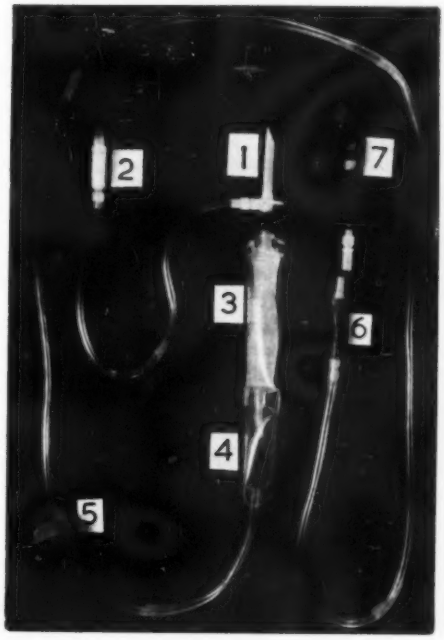

Fig. 2.

1. **Combined piercing-needle and airway.**
2. **Air inlet tube with filter.**
3. **Filter chamber.**
4. **Drip chamber.**
5. **Flow regulator.**
6. **Rubber insert for injections.**
7. **Intravenous needle assembly.**

The chamber immediately below the piercing-needle houses a nylon filter which has a minimum area of 32 sq. cm. (5 sq. in.) and has 55–66 meshes per linear inch.

Below this is the drip chamber, with a drip tube of 4 mm. external diameter. The distance from the end of this tube to the outlet of the chamber is at least 40 mm. Both the filter chamber and drip chamber are easily compressible.

The 125 cm. (50 in.) of plastic tubing leading from the bottom of the drip chamber ends in a short length of rubber tubing and a male Luer adaptor.

The flow regulator is a nylon moulding designed to compress the tubing by rotation of a cam (vide infra).

The external diameter and shaft length of the needle are the same as those of the needle issued with the "standard" glass-rubber set (1·5 mm. and 35 mm. respectively), but the shaft passes through the needle hub, thus increasing the length of the narrow gauge from 35 mm. to 74 mm. The hub, made of plastic, is designed for attachment

to a 40 mm. length of plastic tubing terminating in a female Luer adaptor. This "needle assembly" is packed separately in a glass container in which it is autoclaved so that both the external and internal surfaces of the assembly are sterile. The short length of plastic tubing attached to the needle has the effect of bringing the rubber tubing for the injection of drugs some 2–3 inches from the site of venepuncture. If the needle were mounted directly on to the adaptor at the distal end of the set, there would be more likelihood of displacing the needle or soiling the site of venepuncture when injecting substances into the rubber tubing.

The specification also covers the following points:

1. The *quality of the material*, which must be such that no harmful substance can leach out into the fluid being transfused.

2. *Pyrogen and toxicity tests.*

3. *Sterilisation.*—The equipment must be autoclaved at a pressure of 15–17 lb. per sq. in., at a temperature of 121–123°C for at least 30 minutes. Efficiency of autoclaves must be controlled by spore paper tests on each batch, the papers to be submitted to a competent bacteriologist.

4. *Leakage.*—The set shall not leak under an internal air-pressure of 8 lb. per sq. in. when immersed in water at 30°C for at least 2 minutes.

5. *Self-sealing properties of rubber tubing.*—After puncture with a 23 S.W.G. needle, the short length of rubber tubing incorporated in the distal end of the set for the giving of injections shall be capable of resealing and withstanding an internal air-pressure of 5 lb. per sq. in. without leaking.

Using the Set

When taking any new apparatus into use it is usually well to familiarise oneself with it by trial runs, and we advise new users of the plastic transfusion equipment to practise a few times with bottles of water before giving a transfusion. The technique of using this set differs in certain respects from that of using the glass-rubber set. We reproduce here, with comments, the instructions printed on each container:

1. "Mix contents of bottle by inverting several times."

This is important particularly when transfusing concentrated red-cell suspensions.

2. "Remove sheath from piercing needle by first pushing to break seal and then quickly withdrawing."

The need for pushing, rather than pulling, to break the seal must be emphasised. Failure to appreciate this has resulted in a great deal of unnecessary effort.

3. "Tighten the metal screw cap and force piercing needle all the way through the rubber closure. Do not twist. If necessary, the piercing needle may be slightly moistened with sterile saline to facilitate puncturing."

Swab the top of the bottle and ensure that the metal cap is properly tightened. Should the cap be loose, the rubber closure or wad may sometimes be pushed into the bottle when inserting the needle. Steadily maintained pressure is necessary when piercing the closure, for twisting will occasionally cause the rubber to split, resulting in leakage of the bottle contents between the needle and the closure. Hold the bottle horizontally and push the needle through one of the sectors on the closure marked "2". The sectors marked "1" will have been punctured previously by the needles of the blood-taking set.

4. "Close the regulating clamp and suspend the bottle, at the same time hooking the air inlet filter in an appropriate position. Remove sheath on air inlet filter."

To preserve the efficiency of the air filter it is important to prevent the cotton-wool in the air-inlet tube being wetted by the transfusion fluid. This danger is minimised by ensuring that the distal end of the air-inlet tube is always above the level of fluid in the bottle, and (contrary to the instruction on the box) by not removing the sheath from the air-inlet tube until the regulating clamp is about to be opened.

5. "Squeeze and release filter chamber several times until full."

This must be done gently to prevent frothing and to avoid overfilling the drip chamber (vide infra).

6. "Squeeze and release drip chamber until about one-quarter full."

It is usually found, after filling the filter chamber, that the drip chamber is already sufficiently full, and any further squeezing will result in flooding.

7. "Open clamp on tubing and expel all air—close clamp."

Remember to remove the sheath from the distal end of the tubing. In our opinion, the sheath on the air-inlet tube should be removed just before opening the flow regulator.

8. "Remove sheath from intravenous needle and insert into vein. Join to tubing of giving set by means of adaptors and open clamp."

9. "If flow stops or slows down during transfusion, clamp off tubing below drip chamber, squeeze and release filter chamber. When re-starting the transfusion, make sure that air does not pass down tubing."

This instruction suggests that slowing or stopping of transfusions can always be overcome by this simple manipulation. We refer to this under Special Problems.

10. "In sets so provided, additional medication may be injected through the section of rubber tubing. Do not use a needle wider than 18 S.W.G."

The original specification of the resealing property of the rubber tubing mentioned an 18 S.W.G. needle. This was later changed to 23 S.W.G., and the instructions on the container will be amended in due course.

There are two schools of thought about injecting medicaments via transfusion apparatus, and the small piece of rubber tubing is provided for those who wish to use this route. A reasonable number of injections can be made with a small-gauge needle (preferably not wider than 23 S.W.G.) without danger of leakage, except perhaps when pressure is later applied to the transfusion fluid. Any rubber tubing may leak in these circumstances, but the risk is lessened by inserting the needle obliquely through the wall of the tubing rather than at right-angles. The rubber tubing is sited near the distal end of the set so that substances injected will reach the circulation immediately and with the least possible dilution. In certain circumstances the rubber tubing may be inaccessible to an anæsthetist during an operation, and to meet this contingency plastic extension tubes with adaptors at each end are supplied by the manufacturer.* By using an extension tube, the rubber tubing is brought four feet away from the site of venepuncture.

As the rubber is the part of the set most likely to deteriorate with long storage, it should be examined before use.

11. "Pressure may, if necessary, be applied to the fluid in the bottle via the air inlet adaptor. To prevent reflux of blood on to cotton wool filter, the air inlet tube should be clamped with an artery forceps when the bellows are not being used. Infusion Rate (approximately) 15 drops = 1 ml."

The air-inlet tube is fitted with a female Luer adaptor so that an air-pressure pump fitted with a Luer adaptor mount ensures an airtight junction. To reduce the pressure, the flow regulator must be completely closed and the bottle reverted before releasing the clamp on the air-inlet tube. Air will then pass out of the bottle through the air inlet. We prefer, however, to use a rotary mechanical pump with this set rather than an air-pressure technique (vide infra).

There is a warning printed on the box—namely, "The exterior of this set is non-sterile, except where protected by a sheath." This is emphasised by a caution, printed on the cardboard former, that the set should not be used if any of the protective sheaths are loose.

Apart from the needle assembly, the set, as issued, cannot be handled by a person who is "scrubbed up". Nevertheless, it will withstand autoclaving at 121–123°C for 30 minutes and may, therefore, be sterilised (e.g., in a dressing-drum) for certain specialised procedures such as exchange transfusion. Before autoclaving it is important to remove all plastic sheaths (otherwise the set may collapse), and to pack the set loosely coiled in a drum to avoid kinking. In our experience the nylon flow regulator is distorted during autoclaving and is thus rendered useless.

*Capon Heaton & Co. Ltd., Hazelwell Mills, Stirchley, Birmingham 30. 1s. 1d. each. Minimum order 25.

Special Problems

Many early criticisms were due to lack of familiarity with the new set, but there are some problems which merit further attention.

The Drip Regulator

If the set is to be ready for immediate use in any circumstances, it must include a drip regulator. In its present form this is a small nylon device designed to exert pressure by movement of a cam. In practice, it has proved unsuitable for accurate variation of drip-rates. It tends to be stiff in action, and lubrication has not made any noticeable difference. A new pattern of regulator (fig. 3) gives promise of success. It consists of a plastic channel, about $1^1/_2$ in. long, housing the tubing which is compressed by the movement of a milled wheel, and it can be operated with one hand. Nevertheless, plastic tubing is less elastic than rubber, and consequently a little more trouble may have to be taken before achieving the desired rate of flow. After compression for a long time, manipulation may be required to restore the flattened tubing to its original contour.

Fig 3—New pattern flow regulator.

Until the new regulator is generally available, the metal gate-clip previously supplied with the glass-rubber sets should be used; but this, of course, is not disposable. Where a very accurate and slow rate of flow is required, it is probably always better to use a precision-made regulator such as those described by McAneny (1958) and Morton (1953).

The Bottle Closure

The rubber closure designed to conform with British Standard specification 2463 is issued by the Ministry of Health particularly for use with piercing-needle sets. Soon after the plastic sets came into use, there were complaints of leakage between some rubber closures and the external surface of the piercing-needle—most often when infusing saline and less often when transfusing blood. The incidence of leakage varies from hospital to hospital and it has sometimes been due to the use of other than British Standard closures. As mentioned previously, we advise applying steady pressure when inserting the needle, avoiding any twisting action. The lubricant effect of sterile saline undoubtedly makes insertion of the needle easier and reduces the likelihood of this trouble.

We hope that a slightly modified closure, which will obviate leakage, will be available in the near future. At least one commercial firm preparing crystalloid solutions has plans to introduce closures designed specifically for use with the new set.

The Intravenous Needle

Complaints about blunt needles may be due to occasional batches of sets with poorly sharpened needles being issued to certain hospitals. This problem has been discussed fully with the manufacturer.

It has often been asked why a disposable needle is included with each set when many hospitals prefer to use their own needles or cannulæ. Since 1939 the policy of the Transfusion Service has been to issue a complete set for giving a transfusion in hospital or elsewhere without the user having to provide components such as the needle, except in special circumstances—e.g., when transfusing small children or infants. Most doctors nowadays expect to find a needle in each transfusion set. If many needle assemblies remain unused, their recovery and return to the manufacturer may prove an economy; or it may be worth considering issuing all or some sets without needles, although there are certain obvious objections to this.

Flooding of Drip Chamber

This becomes less likely as one gains experience in using the equipment. Should it happen, the regulating clamp must be closed tightly, the bottle reverted, and blood injected back into the bottle by squeezing the drip chamber. This must be done gently to avoid frothing.

Pressure Transfusions

Although the set has been designed to allow the application of pressure via the air-inlet adaptor, in our opinion a mechanical pump such as that described by Martin (1954) is more effective and safer. Objections to this pump when used with the " standard " glass-rubber set—such as the possibility that air will be sucked through previously punctured rubber tubing (Langmaid and Mushin 1955) or through a partly blocked filter —do not apply with the new set. The Martin pump in its present form needs modification to allow for the difference in the thickness of rubber and plastic tubing. We have modified a number of pumps as follows:

Sleeves are cut from the filter chamber of a used plastic set and these are slightly enlarged by immersion in hot water and stretching with the fingers. While still warm they are fitted over the rollers of the pump and on cooling make a firm grip. A small detachable metal collar is fitted into the proximal anchoring clamp of the pump to ensure that the tubing is held securely.

We understand that Messrs. Allen & Hanburys are exploring the possibility of supplying a kit for the modification of existing pumps and making new models to operate with both types of sets.

We have used the Martin pump to study the pressure built up within the set when blood is driven through the intravenous needle into an open receiver. We find that, when it is rotated very rapidly, pressures of over 40 lb. per sq. in. are produced in the distal end of the lumen of the tubing. With average sustained effort and a pressure recording of 10–15 lb., 540 ml. of blood can be transferred through the plastic set in 1 min. 15 sec. This is enough to meet the needs of any clinical emergency. To test the efficiency of the pump, these investigations were made with blood at 4°C, since at this temperature the plastic tubing is less resilient. Since the effective pressure is governed by the diameter of the narrowest part of the set (in this case, the intravenous needle), over-exuberant use of the pump does no more than build up excessive pressure proximal to the needle. This cannot increase the rate of flow and it exerts unwanted stresses on the set. During pressure transfusions we have observed ballooning of the rubbert insert at the distal end of the set, and it might be well to apply reinforcement collars to prevent the rubber blowing off.

For those who prefer to use the positive-pressure technique, we suggest using a sphygmomanometer bulb to which is attached a short length of rubber tubing terminating in a male Luer adaptor. In our experience, the non-return valve in this type of pressure unit is more efficient than that in a Higginson's syringe. It is important to keep the plastic air-inlet tube of the giving set upright when using an air-pressure pump to prevent wetting of the cotton-wool air filter by the transfusion fluid.

Rate of Flow

Some clinicians have reported difficulty in transfusing more than one bottle of blood through the plastic set. If this were a widespread experience, one would expect the new sets to be used in greater numbers than the old ones; but so far this has not been so.

Laboratory investigations show that 540 ml. of blood at 4°C will pass by gravity through the " standard " glass-rubber set in an average of $5^1/_2$ min. and through a plastic set in 10 min., when the head of pressure is five feet, the regulator is fully opened, and the blood is passing through the intravenous needle into an open receiver.

There is a tendency to attribute this lower rate of flow entirely to the filter of the new set. Our experiments, however, have shown that the needle is largely responsible.

Though its shank length and bore are the same as those of needles issued with glass-rubber sets, the 1·5 mm. bore is carried through the hub of the needle, *thus doubling the length of the narrowest portion of the complete set* (from 35 mm. to 70 mm.). 400 ml. of a solution of fixed viscosity took 10 min. 43 sec. to run through a plastic set with the normal needle attached, whereas with the same head of pressure it took only 6 min. 16 sec. to pass through the same set when the needle was cut down to 35 mm. length.

The pore size of the nylon filter is smaller than that of the metal-gauze filter, and this undoubtedly has a bearing on the rate of flow. On the other hand, less efficient filtration will certainly not benefit the patient. In fact the pore size and area of this filter are greater than those used in most other Continental and American sets, and of the filter that has been considered by the Transfusion Equipment Committee of the International Standards Organisation. We have already suggested that when, in emergency, large amounts of blood must be given, a mechanical pump should be used.

It is said that concentrated red-cell suspensions may block the filter. Filtering the blood when preparing packed cells might overcome this difficulty.

The usual procedure when fixing the tubing to the skin of the arm is to create a loop just proximal to the needle. We have found that, if this loop is too sharp, the plastic tends to angulate at the apex of the curve, even to the extent of stopping the drip. This angulation occurs particularly when the plastic warms up—e.g., when the arm taking the transfusion is inside the bedclothes. One way of preventing it is to make the loop fairly large, but this, of course, shortens the effective length of the tubing.

Other possible causes of slowing of the flow may be blockage of the airway needle or of the blood outlet by small clots. Such obstructions are usually overcome in one of the following ways. The bottle may be shaken a few times. To clear the airway needle, pump air through the air-inlet tube after reverting the bottle. To clear the blood-outlet tube, squeeze the filter chamber several times, remembering to close the drip regulator.

Sometimes the rate of flow can be increased simply by raising the height of the bottle. It should also be remembered that venous spasm offers resistance to the rate of infusion, and this should be taken into account when assessing the efficiency of any set.

Advantages of the New Set

Having drawn attention to possible disadvantages in the new plastic set, we must now refer to its definite advantages.

Thrombophlebitis

The M.R.C. subcommittee (1957) reported a reduction in thrombophlebitis by approximately 50%, and favourable comment has been received since the plastic set came into use.

Disposability

In re-processing a set after use, it is impossible to guarantee that the interior of rubber tubing, glassware, and needles is thoroughly clean and free from pyrogens. We therefore welcome the principle of using a new set for each transfusion.

Air Embolism

The filter in the glass-rubber set is within the bottle, and this introduces the risk of air embolism, particularly when fluids are being transfused under pressure. Should the lower half of the filter become blocked by blood-clot, air may be blown or drawn through the top of the filter (Doyle and Frodsham 1949). Furthermore, when opaque rubber is used, a large volume of air may pass down the tubing unobserved (Langmaid and Mushin 1955). Both these hazards are avoided in the design of the disposable set.

In addition, since all component parts are welded into a continuous line, and the tubing has not previously been used, the risk of air entering the set through leaking joints or punctured tubing is much less.

Risk of Infection

Although the procedure of opening the bottle to insert the bung of the glass-rubber set has in practice proved safe, Michaels and Ruebner (1953) have reported two cases of persistent pyrexia during long-continued infusion through a single set which were possibly attributable to accidental contamination of the crystalloid solutions when changing bottles. Since the plastic set is of the piercing-needle type, the insertion of the set in the bottle carries very little risk of introducing bacterial contaminants. The inclusion of an air filter at the end of the air-inlet tube is a safeguard against the introduction of infecting organisms by this route. Bull and Hurst (1953) have drawn attention to the need for an air filter between the air inlet and the bellows which may be used for giving transfusions under pressure, since the bellows are often found to be contaminated with microorganisms.

Functional Interchangeability

The International Standards Organisation Technical Committee on Transfusion Equipment, recognising that standardisation, however desirable, is not practicable, recommended in 1952 the general adoption of the piercing-needle type of set in order to bring about functional interchangeability. Provided the container is sealed with a perforable closure, a piercing-needle set can be used irrespective of the dimensions of the container, thus making it possible to transfuse, through apparatus prepared in one country, fluids collected or prepared in another. This is not so with the British "standard" glass-rubber set, which can be used only with bottles with a certain internal-neck diameter. Most giving sets used in other countries are now designed on the piercing-needle principle. This principle has been followed by the Army Blood Transfusion Service since 1939 and in the glass-rubber set, introduced by the Ministry of Health in 1953–54, and used by the National Blood Transfusion Service in the Leeds and Sheffield regions. Further extension of the use of the plastic set described in this paper will bring about conformity with I.S.O. recommendations.

Transfusion in Infants

The plastic set may be used as follows for administration of small volumes of fluid to infants:

The seal between the piercing-needle unit and the filter chamber is broken by a sharp twist, and the former may now be pulled apart from the set. After the collar attached to the filter chamber has been removed by splitting with scissors, a burette such as that described by Bewes (1958) or Swain (1958) is incorporated between the piercing-needle and the filter chamber by means of latex tubing. The modified set may be autoclaved complete after removal of the protective caps, or, alternatively, the glass burette with the rubber tubing attached may be sterilised as a separate unit and the modification carried out quite simply at the bedside.

Suggestions for the Future

We are convinced of the desirability of using disposable equipment in transfusion work, and probably plastic is the material of choice. But some improvement in design may be expected.

We have indicated the need for modifications in the design of the bottle closure, the flow regulator, and intravenous needle.

There are arguments in favour of a long airway needle which would pass above the level of the fluid in the bottle, so that air would not have to bubble through the blood. Advantages would be that the air inlet would be less likely to be blocked by small particles of blood-clot, and that rapid transfusions, using the air-pressure method, could be more easily controlled. The cost of providing a long metal piercing-needle in each disposable set would, however, increase the price disproportionately.

A possible alternative to the short piece of rubber tubing for giving emergency injections is a self-sealing rubber diaphragm, supported by a metal retaining cap, connected to the lower end of the set via a nylon T-piece; but we have no experience of this device.

We should like to see a variety of sets offered for special purposes. In spite of the extra cost, some should be available which are sterile on the outside, so that they may be handled along with other sterile equipment. In the interest of economy, some sets could be provided without needle assemblies for use by those who always prefer to use their own needles or cannulæ when giving a transfusion. The different types of sets should be clearly labelled and possibly distinguished by colours.

We wish to thank our clinical colleagues for their comments and experience. Also Dr. W. d'A. Maycock for his helpful suggestions in the preparation of this paper. Our thanks are due to Dr. H. G. Koster for figs. 1 and 2 and to Messrs. Capon Heaton for fig. 3.

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POSTGRADUATE FOUNDATION IN SYDNEY

LAST July the University of Sydney, on the recommendation of the Postgraduate Committee, under the chairmanship of Dr. V. M. Coppleson, established a Postgraduate Medical Foundation. Details announced this week show that the new organisation has some unusual, and perhaps unique, features.

Its objects include the furtherance of postgraduate education and research; and its first objective will be to establish a central fund to aid the faculty of medicine, the postgraduate committee, and the Sydney teaching hospitals in developing research and providing fellowships and scholarships. Its support of research will not be restricted to one institution or department. Because of the country's physical isolation from other world centres, there is a special need for Australian workers to make visits overseas and for overseas workers to visit Australia; and the Foundation aims to further this two-way traffic. The Foundation breaks new ground by planning to extend postgraduate medical education to embrace groups outside the medical profession. Thus programmes will be specially arranged for paramedical groups, such as physiotherapists, nurses, social workers, and technicians, and for community groups, specially informed lay groups, parents, and others.

The first subject to be treated in this way will be the subnormal and physically handicapped child. Dr. L. T. Hilliard, superintendent of the Fountain Hospital, London, is to visit Australia in April, when a medical educational programme will be held in Sydney and Newcastle. This is to include a week's full-time postgraduate course, talks to social workers and physiotherapists, and discussions with the child-welfare department and various other organisations. Talks to parents and friends will also be arranged. At the same time the Foundation will explain publicly by radio and television about handicapped children.

The Foundation is to be financed primarily by admitting to membership persons, firms, companies, institutions, or associations as governors, members, or associate members. The headquarters are at 131, Macquarie Street, Sydney, N.S.W.

HEALTH CENTRES: A NEW PATTERN

AT Oxhey, Hertfordshire, a health centre of a new type has been built. The building consists of two blocks linked with each other: one block is a part-III health centre in which the county council, as local health authority, will provide maternity and child-welfare and other clinics; and the other block contains group surgeries for five doctors built with an interest-free loan obtained under the group practice loans scheme.

The main entrance for those using the local-health-authority services leads to an assembly hall with which the various consultation or treatment rooms are associated. The dental suite has a separate entrance so that dental sessions can be arranged without regard to what may be happening elsewhere in the building—an important consideration should the service become dependent on part-time dentists.

The surgeries have been built by the practitioners on a site acquired by the county council and leased on a ninety-nine-year term. The lease was amicably arranged to ensure that the exterior should be decorated by mutual agreement so as to preserve the integrity of the appearance of the building.

Opening the centre on Jan. 9, Mr. Derek Walker-Smith, the Minister of Health, said that it was an example and an experiment in close cooperation between family doctors and the local-health-authority services.

"The group practice loans scheme", he said, "is not intended to provide a substitute for health centres. But, since its inception, the idea of group practice has widened considerably and there are now a number of cases where group practices approach the health-centre idea by incorporating certain local-health-authority services. The Oxhey health centre represents the extension of this process into a marriage of group practice and the full range of local-health-authority services to create a health centre in the full sense of the word. Its opening demonstrates a new way to achieve the object of integrated services."

NURSES IN FEVER HOSPITALS

THE shortage of nurses in infectious-disease hospitals is discussed by Dr. T. Anderson, regional consultant in infectious diseases, in a report to the Western Regional Hospital Board of Scotland.[1]

Most entrants to training in infectious diseases are aged about 17. Some four out of ten leave, half of them within six months of starting training. Dr. Anderson points out that these girls begin their training earlier than those taking the general training; and it might reasonably be suggested that "trial by immersion" is likely to be no less effective than any elaborate selection mechanism. Nevertheless the figures suggest that a considerable proportion of girls are superficially attracted to nursing but find themselves unable to accept its disciplines—a difficulty which, as he adds, is not peculiar to the fever hospital.

Most of those trained in infectious diseases between the ages of 17 and 18 proceed to general training when they can start this, at the age of 18; and before steps are taken to close the infectious-diseases part of the General Nursing Council Register it would be well to inquire what some of these young women would have done if an early period of training had not been open to them. It seems undesirable that, at some future date, nurses should be regarded as "generally trained" who have not obtained experience of the management of acute febrile illnesses—especially because in future a considerable proportion of infectious diseases may be nursed at home in the houses which are slowly replacing the overcrowded and slum properties. "It seems at least arguable that some centres of nurse-training should exist which can accept girls at an earlier age for limited training—a training, however, which would lead on to general training."

1. Western Regional Hospital Board: annual report on the work of the Infectious Diseases Hospitals, 1957.

The Wider World

AN INDIAN VILLAGE

SUJATA CHAUDHURI
F.R.C.P.E., M.R.C.P., D.C.H.
From the Nizamuddin Village Health Centre, New Delhi, India

THE village of Nizamuddin lies just outside New Delhi, to the south-east. Of its eight hundred families, rather over a hundred were covered by a survey in 1956–57. The people belong to three religious communities—Moslem (66%), Christian (20%), and Hindu (14%). The village

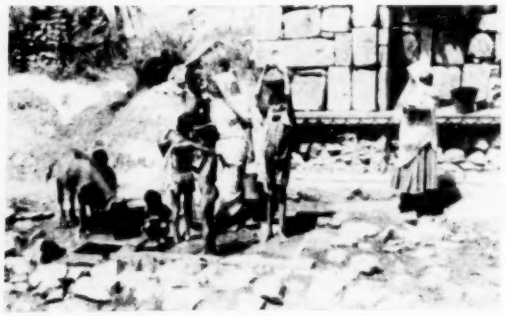


Fig. 1—Only water-tap, used by nearly 200 families. Note buffalo calf sharing bucket of water.

is a place of pilgrimage for Indian Moslems, for it was named after their great saint, Nizamuddin Aulia, who lived in the 13th century.

Being close to a large city, and not being an agricultural village, Nizamuddin resembles the back streets of a town. Most of the inhabitants are very poor, and (with a few exceptions) poverty keeps their homes dirty. In most dwellings the average floor-space is less than 20 sq. ft. per person. Many householders share their premises with relatives or acquaintances. The village has open drains and no sewer.

Of the families surveyed, nearly 70% have some kind of regular income; about 20% have only occasional earnings (e.g., as labourers, or masons, or in selling poultry and eggs); while the remaining 10% are unemployed. In the absence of piped water, many of the youngsters and able-bodied men earn a little money by carrying water for those who can afford to pay for it. The people with most money are businessmen, Government employees, and the priests

Fig. 2—Typical houses. The nurse's morning call.

who rent out houses. In our survey the earnings of 70% of the families with a regular income were:

Rupees per month *	*Percentage of families*	*Rupees per month* *	*Percentage of families*
25–50	16	151–200	7
51–80	46	201–300	5
81–100	6	301–400	4
101–150	16		

* The exchange value of the rupee is about 1s. 6d.

The Constitution of India requires the State to secure a "living wage" for all workers—agricultural, industrial, or otherwise. There is so far no official definition of the term "living wage". Perhaps, however, it can be construed as one which ensures "a decent standard of life, with full enjoyment of leisure, and of social and cultural opportunities".

At present price levels, a balanced diet for one adult costs at least Rs. 1·5 a day (Rs. 45 a month); and the minimum total requirement, including food and clothing, is about Rs. 60–70 per month. Since the average family consists of 5·5 persons and may be regarded as equivalent to 4 adults, the minimum requirement works out at about Rs. 250 per family per month. According to our survey some 93% of the families earned less than this amount, and nearly 75% of them earned less than half of it.

Fig. 3—Children in rags, mother, and father visiting the health centre.

Most of the people being illiterate, family planning can hardly be expected. Here are our average figures for the families:

No. in family, 5·51 living; no. of sons 1·98 living; 0·56 dead. No. of daughters 1·53 living; 0·46 dead. No. of stillbirths 0·19 (3·7% of pregnancies). No. of miscarriages 0·31 (6% of pregnancies). No. of pregnancies 5·20 per married woman.

The following are the figures for pregnancies in 89 women:

No. of pregnancies	*No. of mothers*	*No. of pregnancies*	*No. of mothers*
14–16	2 (2·2%)	4	10 (11·2%)
11–13	3 (3·3%)	3	7 (7·9%)
8–10	17 (19·2%)	2	14 (15·8%)
5–7	29 (32·5%)	1	7 (7·0%)

Nearly all the mothers in this community are again pregnant within two years of a childbirth.

Not included in our survey are many families—in one area about sixty—who have a miserably crowded existence in some houses resembling barracks. They depend on the maternity health centre at Bhogal (two miles away) and they badly need a day-and-night maternity service on the spot.

The staple diet of the people is wheat and pulses. Very little milk is consumed, and, though they are not vegetarians, they can rarely afford to buy meat, fish, or eggs.

Fig. 4—Children of the nursery school enjoying the morning glass of milk. After a year's study they are growing into healthy and proud citizens.

The diet is deficient in leafy vegetables, fruits, and nuts, and the intake of fat is below normal, the average being about 25 g. per day per adult.

Most of the villagers—especially the women and children—are lethargic and pale, with signs of mild vitamin deficiencies such as angular stomatitis, soreness of tongue and buccal mucosa, xerophthalmia and xerosis of skin, and (in a few cases) spongy gums. Skin infections, respiratory infections, and intestinal worms are very common.

Blood was taken by fingerprick from a hundred women and children. In each age-group the average values, both for hæmoglobin and red cells, were below the average normal. In the first five years of life, individual figures were as low as 3 g. hæmoglobin per 100 ml. (Adams-Sahli) and 2,500,000 red cells per c.mm.; but in the second five years they were rather better, because older children can fend for themselves and may earn money.

The average figures for females of 10–40 years of age were 10 g. Hb and 3,200,000–3,600,000 red cells. Higher levels were found at 50–60 years of age when there is normally no loss of blood from menstruation or childbirth. No malarial parasites were found in the blood-smears. The anæmia was normocytic, normochromic, or hypochromic.

The blood of men could not be examined, because most of them are out at work for the whole day. Their health is on the whole much better than that of women and children.

* * *

In this village poverty, ignorance, and age-old superstitions combine to prevent improvement of hygiene. While undernutrition and malnutrition are responsible for the poor physical condition of the people, even more important as a cause of ill health may be the overcrowding and insanitary living conditions which favour spread of infections.

In England Now

A Running Commentary by Peripatetic Correspondents

Is any capital of Europe worse paved than Athens? In the neighbourhood of Socrates Street, the roads are cobbled and the footways have large irregular convex stones laid in the manner of crazy pavement, so that when it rains they form stepping-stones among ponds. The pedestrian must resist the temptation to gaze at the gleaming white marble on the Acropolis, for there is a further menace in open cellars, with no barrier or warning, ready to receive Johnny-head-in-air within their dark depths. Lorries, trams, barrows, and donkeys block the narrow ways, and swift gleaming cars of bright colours dart in and out. One of our party tripped over a tramline and fell full length in the path of Juggernauts from four directions. No harm was done beyond a few bruises and a broken wrist-watch; the traffic, though alarmingly inconsequent, seems less ruthless than that of Rome or Paris.

The markets were open from early morning till late at night, crowded with buyers who did not diminish the piles of vegetables and fruit brought in each day, as in classical times, from surrounding Attica: apples were in great variety and an overall brilliance was given by the mountainous heaps of oranges. Since it was Christmas time, live turkeys, with legs tied together, lay placidly on the ground in odd places. Their purchasers returned and carried them home like babies in arms.

Shopping was complicated by the Athenian measure, the oke, which roughly equals 2 lb. 12 oz. and is divided into 400 dramia. We did not attempt to master it, and when we went to buy sweets at a kiosk we presented a piece of paper marked 750 g. This was unacceptable to the smiling girl in the kiosk who invited us to say "how many," and finally counted out 25 boiled sweets wrapped in coloured paper and picked the money out of a handful of small change.

Olives were easier; two large barrels of olives of different degrees of blackness stood on the pavement outside an open shop. A young man with a scoop was filling paper bags for customers. We pointed to the less dark olives and said: "the same as his." Our filled bag was handed into the shop over a barrier of stacked kippers and in due course a paper with the price on came out.

Shoelaces were an insoluble problem. Our phrase-book, although it has a section "at the shoemaker", does not give the word for laces, just as "at the post office" does not mention stamps, nor "at the tobacconist" matches. In Rhodes in the Turkish town, however, we found a street of the shoemakers. Many of the shoes and boots hanging outside the shops were of local type, a pull-on thick leather ankle or knee boot, but there were also laced shoes, and we went in. I pointed to my knotted ineffective strings and the proprietor instantly tore the laces out of a show pair of shoes, and handed them to me for a drachma.

We met a "new" tranquilliser, a legacy of the Turks to Rhodes. Middle-aged and elderly men sat outside the cafés playing with circular strings of yellow opaque lumps, probably amber. They were short strings, 9–12 in. in diameter; the owner sat talking, or not talking, just playing with them in an abstracted sort of way. They are called "pass the time" and we saw none in the hands of women, who no doubt have no time to pass.

* * *

Having owned a television set for one month, I feel, to paraphrase Wellington, that it may not frighten the children, but, by God, it frightens me. Gangsters kicked in the teeth (double dose of Humphrey Bogart over the Christmas holiday), corpses hanging upside down (*Love from a Stranger*), shooting, and murders galore. My wife now wakes screaming at night. She's lucky; at least she manages to fall asleep first. Please Dr. Himmelweit, how about investigating the grown-ups?

And as for the effect on homework—where's that paper I was supposed to finish by Jan. 1?

* * *

Punch now has a weekly competition, with tasks ranging from inventing new joke situations to parodying publications and people. How about *The Lancet* starting something similar? The latest *Punch* competition calls for a prophecy of 1959. I was mulling this over during a lecture the other evening, and reached my own conclusions. As I have some inside information (for joke see later), and as I am myself one of the protagonists, I feel it would be unethical to publish the prophecy in a lay magazine; so I offer it to *The Lancet*, competition or no.

In 1959 I am going to win a Nobel prize. I have always known that I would do so one day; but I could never quite see why. Now I know. For a long time I have been trying to devise a means of making a firm diagnosis of Meckel's diverticulum. It can be done with barium meals, but not often. As the mucosa of these wayside houses of ill fame is "gastric", it seems that it might be useful to concentrate on the secretion of acid there. For some time I have been seeking a radioactive isotope which would be excreted in the juice. The outline of the diverticulum could then readily be mapped with a Geiger counter. Of course the radiation from the stomach might cause interference, but that organ can easily be marked out separately by the use of sodawater and a stethoscope. Lately people have become scared of using radioactive materials; so I was doubtful about the Geiger counter; and half way through the lecture I had a better idea. If there are soon to be satellites round the moon taking pictures of her backside, it should not be beyond the ingenuity of modern science to make a miniature satellite which could be swallowed and which would take photographs of the inside of the alimentary tract all the way down. These photographs would be stored up on microfilm to be read at leisure. The only trouble would be to make sure that the satellite is recovered. I solved that before the lecture finished, too. It is easy to fit a nose-cone which on re-entering the Earth's atmosphere would give audible warning of its approach, thus reminding the patient to stop and retrieve it before pulling the plug. I shall enjoy my visit to Stockholm.*

I don't think that anyone has ever received two Nobel prizes in one year, or shared the award with himself, so I will reserve my other item for 1960. This year some people were honoured for inventing sex in microorganisms. My Nobel prize in 1960 will be for my useful work in fitting bacteria with contraceptives.

* * *

My nephew John is a medical student. He is a progressive young man and he spent much of his last summer holiday in Sweden visiting their splendid hospitals. Last week he developed appendicitis and was admitted to a famous English teaching hospital where the offending organ was removed by a surgical personage. In a letter John told me that he was doing very well. He added, "But this is rather a backward place; do you know, they have not got an artificial kidney."

* * *

The Mole must go by Underground
And seldom takes a bus.
If he gets in an Edgware train
He never makes a fuss.
He makes his own connection
And goes to Mill Hill East,
He sometimes meets a worm en route
And has a scrumptious feast.
I would exchange my Army mess-kit
To be a Mole in a moleskin weskit.

* If our peripatetic correspondent is the decent chap we think he is, he may wish to give part of his Nobel prize to the designers of the little pH-endoradiosonde described in our columns a year or so ago (*Lancet*, 1957, i, 1224).

Letters to the Editor

THE CLIMATE OF MEDICAL EDUCATION

SIR,—Many of those who have read Professor Arnott's stimulating address (Jan. 3) will have pondered on the possible implications of the innovations he advocates. These include a drastic reduction in the number of theoretical lectures and their replacement by a highly developed tutorial system. At the same time there should be a move towards integrating our medical schools within residential universities.

If one considers why the education of the medical student should be confined within a restricted number of hospitals within a single city in each region, one cannot avoid the conclusion that it is not entirely because of the traditions of these hospitals, nor is it entirely because of the excellence of their medical staff; it is largely because the formal theoretical lectures, believed to be an essential part of the training of a doctor, are held in or in the vicinity of these hospitals. It is also, though no doubt to a lesser extent, due to the necessity for students to attend a hospital within easy reach of their homes or where congenial lodgings may be found.

Professor Arnott's suggested relegation of the lecture course to a less dominating place in the curriculum will materially weaken the most important tie binding the student to one or a group of hospitals. Is not this a suitable opportunity to consider whether there is not some case for decentralising the education of the medical student?

Anyone who has travelled extensively through the far-flung hospitals of a region cannot fail to be aware that there are in some of these hospitals not only a rich clinical material but also consultants of great ability and experience—men whose breadth of culture and personality would make them excellent tutors in the sense implied by Professor Arnott.

Those of us who were forced by the closing of teaching hospitals during the blitz to seek instruction at non-teaching hospitals will remember how refreshingly practical and straightforward was the instruction we received from "amateur" teachers at these hospitals, and the pains they took to help us. However, the war ended, the theoretical lecture was reinstated, and the students returned to the fold, where teaching was again confined to a handful of men not always of very great experience.

May I therefore suggest that Professor Arnott's suggestions be carried a stage further and that the universities recognise as teachers (or tutors) men of distinction or ability in the hospitals remote from the medical schools. In this way the choice, not only of clinical material, but also of excellent teachers would be greatly increased and the staff of the peripheral hospitals would no longer be denied the stimulus that medical students provide.

Students might be attached for two or three months to these "teachers", carrying out their clerking in the way suggested by Professor Arnott. It is true that it will be necessary for accommodation to be provided for students at these peripheral hospitals, but perhaps some of the funds to be used for the halls of residence could be set aside for this. As for the loss the student will suffer during the short period he is away from the cultural centre, it is true to say that there are few parts of England unable to make a cultural contribution to those eager to receive it.

It is to be hoped that the suggestions I have made will be taken seriously; much good may be gained by all

concerned if the barriers between teaching and non-teaching hospitals are rendered a little less distinct.

Smethwick Hospital. A. L. WOOLF.

MENTAL HEALTH BILL

SIR,—I hope no-one will interpret this letter as representing reaction on my part to the spirit of the new Mental Health Bill, which I welcome in so far as it recognises that treatment of mental disorder, when it cannot reasonably be arranged voluntarily, should depend on medical recommendations and relatives' applications rather than magistrates' orders (except in the case of mentally disordered persons brought before the courts). I welcome, too, the attempt to replace the present separate Acts covering the care of the mentally ill and the mentally defective by one Act embracing both forms of mental disorder. However, it is in this attempt to deal with mental defectives on the same footing as the mentally ill that I feel the Bill is most open to criticism and accusations of unrealism in its approach.

I note with considerable misgivings the sections dealing with the care of the subnormal patient (feeble minded in the present classification). If I have read these sections correctly, in future it will be impossible to admit and to detain in hospital under the proposed "application for admission" procedure a subnormal patient over the age of 21, nor to continue his or her "medical treatment or other special care or training", which by the Bill's definition he requires, past the age of 25, unless it can be shown that he or she "is likely to act in a manner dangerous to other persons or to himself" if released from hospital. It has never been my experience that patients of this type suddenly cease to be subnormal at the age of 25 and equally suddenly cease to require hospital care and supervision for their own protection. The bolder among us may, of course, interpret this need for continued care and supervision as constituting potential danger to the patient if discharged from hospital, but before so doing let them remember the difficulties in which we all found ourselves not long ago through our too wide interpretation of the circumstances constituting "neglect" of a mental defective.

I am concerned also with the proposal that all patients shall be discharged automatically from hospital care after six months' "leave" (which is to replace the present licence procedure in the case of defectives). I hope to publish shortly the results of an inquiry I conducted into the subsequent histories of 52 patients who were recommended for discharge from mental-deficiency orders after eighteen months on licence, as the result of the memorandum H.M. (56) 25, which stated that the Board of Control "would normally expect that a patient should be discharged after a trial on licence for twelve months at most unless there are overwhelming reasons to the contrary." Briefly the results were as follows: in 36 cases the subsequent history was satisfactory; in 12 it was completely unsatisfactory (e.g., illegitimate births, prostitution, attempted suicide); and in 4 cases it could at best be described as "precarious". It seems unlikely that the shorter period proposed will reduce this high percentage of unsatisfactory behaviour after release. It is true that some of these patients might possibly be placed under the guardianship of the local authority before the six-month period expired, but this would depend on the cooperation of relatives, which might not be forthcoming, and guardianship would not in any case be possible in the case of subnormal patients over the age of 21, who are likely to constitute the majority.

Perhaps, I have misread the proposals. If not, I hope that the relevant sections of the Bill will be amended before they become law, because as they stand they seem to preclude the continued care and training of just that group of patients most in need of and likely to benefit from it, and to make it probable that the results of prolonged and painstaking effort by hospital staff will be destroyed in an instant by premature release; for let us make no mistake about it—the care and training of the subnormal must be prolonged and may even then be unsuccessful, and the problem of subnormality can never be solved by pretending it does not exist.

Bristol. W. A. HEATON-WARD.

INDUCTION OF LABOUR

SIR,—I would like to comment on Mr. Theobald's article last week.

In discussing postmaturity as an indication for induction of labour, he assesses the risk of death to the postmature fœtus at a conservative estimate of 4% in this country. Even if this figure represents an arithmetic mean of the series quoted, these cannot represent a reasonable sample of the country. Mr. Theobald cites a very low mortality with the use of free induction in the postmature, but has no control group from which to draw any possible conclusion.

The reward gained by the induction of labour in patients with a free head has not been clearly shown. Finally it is difficult to follow the reason for the conclusion that intact membranes are the greatest single hindrance to normal delivery and the suggestion that routine induction of labour at the end of the 38th week of pregnancy will become inevitable.

Mile End Hospital, London, E.1. E. C. WOOD.

ANTIBIOTICS AND THE COMMON COLD

SIR,—In his laudable anxiety to deprecate the widespread use of antibiotics without serious indications, Professor Garrod (Jan. 3) misrepresents what I wrote (Oct. 4) on the control of the full course of the common cold. I referred twice to the dangers of continuous or widespread use of antibiotics in the treatment of the common cold, and, by implication, supported this general principle. My main purpose, however, was to recount a personal experience which I believed to be of interest to the profession, and, on that basis, I suggested that the tentative and judicious use of a small total dose of antibiotics (e.g., 1·5 g. chloramphenicol and 0·75 g. tetracycline) might be tried in suitable selected cases for the strictly limited purpose of preventing a cold developing to the stage of bacterial invasion. The number of cases in which this method can be tried with any hope of success seems to be severely limited by the condition that the symptoms of an undoubted cold must be reported and the drugs obtained within 12 hours of its onset. This is surely very different from Professor Garrod's version that I "advocate" antibiotic treatment of a cold for the "privileged few".

Professor Garrod protests against giving a dangerous drug (chloramphenicol) "merely for the relief of passing discomfort". The hazard associated with such a small total dose of chloramphenicol is, I believe, virtually negligible, but, in any case, his dictum grossly understates the possible effects of a cold in some people. Repeated colds can be lethal, for instance, in lighting up bronchitis and initiating pneumonia in not a few elderly persons. For such persons, as well as others, the risks associated with a fully developed cold are far greater than those incurred by taking about 2 g. of an antibiotic. He suggests that penicillin might be tried instead of a broad-spectrum antibiotic, but I very much doubt if it would be so uniformly effective; and even penicillin, in these days, carries a small risk of inducing dangerous sensitivity reactions.

The question is primarily one of clinical medicine. Physicians are unlikely to be impressed by the bogy of £112,000,000 being added to the national drug bill; in any case nothing remotely approaching that follows from my argument. Nevertheless I would point out that the 24-hour period of prophylactic treatment in strictly selected cases which I suggested is an entirely different proposition from that put forward by Dr. Sulman (Dec. 20) for treatment of the common cold with chloramphenicol over several days and at unspecified stages.

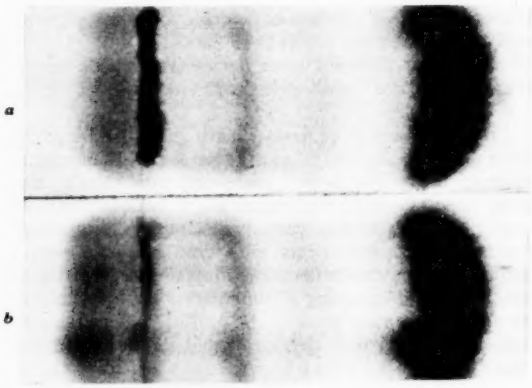
Leatherhead. H. STANLEY BANKS.

DEFIBRINATION SYNDROME IN PREGNANCY

SIR,—The very interesting paper of Dr. Sharp and his colleagues (Dec. 20) reports the investigation of 4 cases of coagulation defect associated with accidental hæmorrhage, and suggests that " in the early stages of this syndrome poor reactivity of fibrinogen to thrombin may be an important feature ". This suggestion is made on the basis of a discrepancy between the thrombin clotting-time of plasma-fibrinogen and the chemical estimation of fibrinogen (using a micro-Kjeldahl method and calcium to initiate the clotting process). Whilst " poor reactivity of fibrinogen " may occur in some patients, we have not observed it at St. Mary's Hospitals, Manchester. We have estimated fibrinogen levels on 459 occasions in 254 patients (using a method in which plasma is clotted by the addition of thrombin and the colour developed with Folin and Ciocalteu's reagent measured [1]), and we have detected 50 patients with low or falling fibrinogen content.

The first stage of this method is similar to the " thrombin-time test ". It is our practice to observe closely the time and degree of clot formation, since, after a little experience of the method, it is possible to estimate the probable fibrinogen level, thus allowing appropriate action to be taken early. Although the clot is usually removed from the test-tube after 20 minutes, on many occasions replicate tubes have been left for as long as 24 hours with no significant increase in the amount of the clot. Using this method, high fibrinogen levels are not obtained when the thrombin clotting time is prolonged, and the levels obtained by this method appear to reflect accurately the severity of the coagulation defect. Furthermore, in a number of cases we have observed electrophoretic patterns suggesting an unequivocal fibrinogen deficiency (see figure), as Kimbell and Ghosh [2] showed in their patient.

1. Varley, H. Practical Clinical Biochemistry; p. 193. London, 1958.



a

b

(*a*) Electrophoretic pattern of a normal plasma (fibrinogen 370 mg per 100 ml.).

(*b*) Plasma from a patient with a fœtus retained 6 weeks after intrauterine death (fibrinogen 134 mg. per 100 ml.).

The authors give a normal range for plasma-fibrinogen (150–300 mg. per 100 ml.), which is too low for the last weeks of pregnancy. It has been shown that the level of fibrinogen increases during pregnancy.[3 4] In our series the mean value between 34 and 40 weeks was 492 mg. per 100 ml. (S.D. 99 mg.). Levels of the order of 200 mg. occurred only in patients in which a previous estimation had been higher, so that, in our experience, such a level is indicative of an early coagulation defect.

We have also carried out a test similar to the estimation of the thrombin titre, and the dilution at which a clot can be seen seems to us to reflect the fibrinogen level of the plasma. Similarly, the one-stage prothrombin-time also varies directly with the fall and rise in the fibrinogen level.

We have been unable to estimate A.H.G., factor V, &c., on many patients, but in 5 of the more chronic cases (i.e., associated with retention of a dead fœtus) no abnormality of these factors was detected.

We would agree that there is a thrombocytopenia in some cases and that active fibrinolysis cannot be demonstrated. The many reports of lysis which have been made have been prompted by the wrong interpretation being placed on marked contraction of poorly developed clots.

Saint Mary's Hospitals for Women and Children, Manchester. R. F. JENNISON.

NORETHANDROLONE IN ACUTE RENAL FAILURE

SIR,—I refer to the preliminary communication by Dr. McCracken and Dr. Parsons (Oct. 25). A further three patients with acute reversible renal failure, following complications of late pregnancy, have been investigated; all recovered. They were given 30 mg. of norethandrolone (' Nilevar ') per day, instead of 80 mg. per day; otherwise the procedures were the same. The table shows that protein catabolism was reduced to about the same degree as with the higher dosage. In case 3 the period of oliguria was unduly protracted and the steroid was given for only four days, yet the rate of urea production remained at the same low level for a further five days, when investigations ceased because renal function was beginning to recover.

REDUCTION OF PROTEIN CATABOLISM

Case	Age (yr.)	Diagnosis	Mean daily urea production (g. N_2)	
			Control	Norethandrolone
1	26	Toxæmia of pregnancy with hepatic necrosis	8·0	3·6
2	37	Accidental hæmorrhage	8·6	2·5
3	36	Accidental hæmorrhage	7·4	3·1

Your leading article of Oct. 25 mentions that testosterone might be a suitable alternative to synthetic anabolic steroids. The following evidence suggests this may not be true when anuria has an obstetric cause. Two patients, who were later shown to have bilateral cortical necrosis of pregnancy, were given testosterone propionate 100 mg. daily. In one patient the rate of production of urea was *not* affected, yet subsequent administration of norethandrolone, 80 mg. per day, halved the rate. In the other patient testosterone did reduce the rate of urea production, but not to the same degree as that usually observed with norethandrolone.

Your leading article and subsequent correspondence (Nov. 15 and Nov. 29) emphasise the high price of synthetic anabolic steroids. However, there is another aspect to consider. As norethandrolone reduces protein

2. Kimbell, M., Ghosh, A. K. *Lancet*, 1956, i, 82.
3. Kennan, A. L., Bell, W. N. *Amer. J. Obstet. Gynec.* 1957, **73**, 57.
4. Scott, J. S. *Brit. med. J.* 1955, ii, 290.

catabolism in the obstetric case, treatment with the artificial kidney is delayed and renal function may recover before the time for dialysis is reached. In our unit this has happened many times, and as the equipment used for one treatment on the artificial kidney costs at least £6 (£25 for some other types of machine in use elsewhere), a considerable saving is achieved. A few patients have been managed successfully in their own hospital, and this has saved the expense of transporting them to our artificial-kidney unit.

Until an equally effective and cheaper drug is available we feel compelled to advise the use of norethandrolone, 30 mg. per day, in acute renal failure from obstetric causes.

Metabolic Disturbances in Surgery Research Unit,
The General Infirmary at Leeds. F. M. PARSONS.

MEDICAL ASPECTS OF ADOPTION

SIR,—I should like to comment on the article by Dr. Black and Dr. Stone (Dec. 13), as the kind of policy they advocate resembles that which has gradually been evolved over the past year in the adoption society in which I work. I should like to describe how it has become possible, with the help of a team of interested specialists, to bring the skill of the appropriate expert to bear on the two main problems of adoption work—namely, the assessment of the suitability of babies for adoption, and of couples for adoptive parenthood. There are in practice considerable problems in working out such a team approach between a voluntary adoption society and medical practitioners and specialists. Our experience, however, would suggest that this can be done where all concerned are aware of the kind of difficulties discussed by Dr. Black and Dr. Stone, and where doctors are willing to give what may be a considerable amount of their time gratuitously, since the Adoption Laws preclude an adoption society from charging fees. I believe that an essential part of such a team approach is that doctors can be fully confident that the social worker has obtained full permission from all concerned before a medical opinion is requested, and that the confidential nature of such medical information will be fully respected and not shared with non-professional persons.

In the assessment of the child, Dr. Black and Dr. Stone most rightly stress the importance of the past history and of the familial history. To cover this in our society, we send detailed social histories and health records to all pædiatricians examining a baby for adoption. Where there is any serious medical condition in the family a full medical report is obtained from the appropriate doctor. Obtaining the detailed histories required for this does, however, necessitate considerable case-work skill and enthusiasm, involving not only an awareness of the delicacy of the matter but also the ability to assess the reliability of the testimony. Often the only witness is the mother herself, though frequently we can also meet fathers, grandparents, and siblings. This kind of assessment may be facilitated in our organisation because we operate not only as an adoption society but in fact primarily as an agency providing a case-work service for single parents, and thus contact with parents who place their babies for adoption may last over several months. Once all this information is obtained, an assessment is made of the potential health problems, both physical and mental. All such details are referred to a pædiatrician to be used in his assessment of the potential of the baby for normal development. We are fortunate in that one of the pædiatricians frequently asked to do such examinations has become particularly interested in our work and has studied carefully the problems involved in making such assessment and prognostication. Where there are medical problems he undertakes to see the prospective adopters and to explain these to them. In this his policy is in keeping more with the view stated in the letter of Dec. 27 by Professor Illingworth than the policy advocated by Dr. Black and Dr. Stone. Such a service by a pædiatrician is invaluable and is of course quite outside the province of the social worker. Furthermore, it has in practice proved most reassuring to adoptive parents.

Where there are complex problems of instability, psychiatric disorder, mental defect, &c., in the family history, the whole problem is referred in detail to the University Department of Psychological Medicine for an assessment of the psychiatric and genetic factors relating to suitability. The decision as to whether a particular child is adoptable from a medical point of view is thus not one taken by this adoption society. It is a decision referred to the appropriate expert, though the adoption society remains responsible for obtaining the background information relevant to such a decision. The further medical examination of the baby after three months, before its adoption is legally finalised, has so far in our society been done by the adoptive parents' general practitioner, except that where there have been any medical complications the original pædiatrician has again examined the baby.

The assessment of the suitability of any couple for adoptive parenthood is equally complex. In this society it is undertaken by an almoner who is also a psychiatric social worker, and by a social case-worker with a special qualification in child care. We have at least three interviews with all applicants, the first with the couple together and then one with each of them alone. From each a full personal history is obtained, together with a personal and family health record. An up-to-date medical report on each is required, and reports are also obtained from any specialists recently consulted. Permission is also obtained to consult with the specialists that the couple may have approached with regard to their inability to have children. All this medical information is invaluable in building up gradually a total picture of any couple, their stability, their mutual adjustment, their attitudes to infertility, and so on. We also try to assess them as to the quality of their personalities, and to anticipate how flexible and understanding they would be as adoptive parents. Where medical reports are not unreservedly favourable these are referred, under initials only, to the society's medical referee, a consultant physician, for his opinion.

Out of 75 applicants to our society who were interviewed as prospective adoptive parents over the recent ten months, 5 were rejected on health grounds, 13 on grounds of personality and adjustment, and a further 5 where both health and personality were considered adverse. These numbers do not include all those rejected initially on the ground of age. This, I think, indicates a fairly high rejection-rate—approximately a third. Of 41 babies whose adoption was requested over the same ten months, an assessment of the psychiatric factors relating to suitability was obtained in 6 cases and of these 3 were considered not adoptable. The placement of 4 others was delayed on health grounds.

Dr. Black and Dr. Stone conclude that information about a child's parents is frequently inadequate because general practitioners are reluctant to give information to children's officers and non-medical committees. Our experience suggests two things. First, that it is possible to obtain the full cooperation of medical practitioners if the social worker and doctor can work together with a common objective and as if in a team, with each recognising the contribution of the other. Secondly, we suggest that such a team approach is much more telling diagnostically than the suggestion of Dr. Black and Dr. Stone that a doctor should sit on the adoption committee, although this of course would always be welcomed. The detecting of potential medical problems we have found to be an integral part of the case-work process and has to be done much earlier than the committee stage of an

application. May I suggest that adoption work particularly well illustrates the interdependence of medical and social problems. The need as we see it is for some kind of administrative machinery to facilitate on a wider basis the kind of team approach here described.

Guild of Service for Women,
21, Castle Street,
Edinburgh, 2.

ALEXINA M. MCWHINNIE
Director.

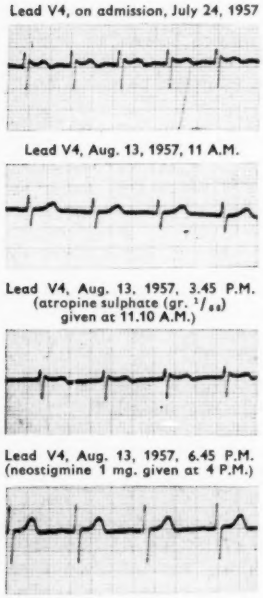
RESEARCH IN CRIMINOLOGY

SIR,—Your annotation of Jan. 3 is welcome and timely. While one would not wish to defend a facile and dogmatic identification of crime with disease, medicine, not only in the field of psychiatry, has much to offer to and gain from studies of criminal behaviour. It is all the more regrettable then that students of medicine at one of the senior universities should be denied the guidance and leadership of a formal university appointment in criminology. We already lag far behind the Scandinavian countries in this field, and our need is for more, not fewer, centres of study where different disciplines can make their contribution to the knowledge of causes and effects of crime. Would anyone seriously suggest that a chair in history in Camford should be abolished because there is one in Oxbridge?

Crowthorne, Berkshire. PATRICK G. MCGRATH.

EFFECT OF ATROPINE ON THE HEART-RATE

SIR,—Dr. Morton and Dr. Thomas, in their most interesting article of Dec. 20, have related the variability of this effect to the total dose, the route of administration, and, in the case of intravenous administration, the rate of administration, and they maintain that this is due to the resultant of its effect on the vagus centre and the vagal nerve-endings. They stated that a therapeutic dose—for example, gr. $^1/_{100}$ (0·6 mg.)—would more consistently cause tachycardia if subjects were already under the influence of a small amount of the drug.


Lead V4, on admission, July 24, 1957
Lead V4, Aug. 13, 1957, 11 A.M.
Lead V4, Aug. 13, 1957, 3.45 P.M. (atropine sulphate (gr. 1/66) given at 11.10 A.M.)
Lead V4, Aug. 13, 1957, 6.45 P.M. (neostigmine 1 mg. given at 4 P.M.)

In a recent case, reported by my colleague and myself,[1] an acute confusional psychosis resulted from the routine administration of 1% atropine sulphate drops in the treatment of retinal detachment in a woman of 33. This psychosis was accompanied by myocardial changes giving rise to considerable concern.

The patient was having a minimum of atropine sulphate gr. $^1/_{110}$ twice daily instilled into the conjunctival sac over a period of $3^1/_2$ weeks. It is considered that the whole of this dose was absorbed, probably by the swallowing of atropine-laden tear fluid which reached the pharynx via the lacrimal passages. The rate of absorption into the system was therefore slow but the cumulative dosage may have been considerable.

On admission, she had a pulse-rate of 150, and an E.C.G. taken when she had settled in bed showed a sinus-rate of 130 (see accompanying figure). In addition, however, the elevation of the S–T segment and diphasic T wave suggested a toxic state of the myocardium. Three weeks after cessation of the atropine administration, the E.C.G. changes had disappeared, the patient's mental state was normal, and the sinus-rate was just below 100, which is understood to have been the patient's normal pulse-rate.

10 minutes after the second tracing had been taken, the patient was given atropine sulphate gr. $^1/_{66}$ (1 mg.) by subcutaneous injection and psychotic symptoms similar to those which she had on admission recurred and persisted for a short period. The point of interest here, however, is that a further E.C.G. tracing taken $4^1/_2$ hours after the atropine administration (see figure) showed a reproduction of the toxic myocardial changes without any alteration in the sinus-rate, which remained at just below 100. 1 mg. of neostigmine was given subcutaneously $4^3/_4$ hours after the atropine administration, and a final E.C.G. taken $2^1/_2$ hours later showed that the myocardial changes had once more resolved.

It would seem, therefore, that in addition to the two sites of action (the vagal centre and the vagus nerve-endings suggested by Dr. Morton and Dr. Thomas) atropine may have a direct effect upon the myocardium or its blood-supply when given in therapeutic doses, without any evidence of alteration in sinus-rate. This is indicated by the E.C.G. findings after the single dose of atropine. The E.C.G. findings on admission, however, when the patient was in a state of chronic atropine intoxication as evidenced by the psychosis, supports their contention that tachycardia would result from repeated small amounts of the drug, since an increase in sinus-rate did not occur after the single dose despite the myocardial change.

Three Counties Hospital,
Arlesey, Beds. J. P. BAKER.

PLEURAL BIOPSY IN THE DIAGNOSIS OF PLEURAL EFFUSION

SIR,—May I add some comments to the valuable paper by Dr. Mestitz and his colleagues (Dec. 27)?

Dr. Mestitz did a number of cases in the Reading area early in 1957, and we were so impressed by the results that pleural biopsy became part of the routine investigation of pleural effusions. My personal experience extends to 40 cases over a period of eighteen months. These numbers are, perhaps, too small for any statistical conclusions, but certain main points are worth emphasising.

The principal value of the method lies in the field of tuberculous and malignant pleural effusions. In my small series, 6 out of 8 tuberculous cases were positive. This rate of 75% is twice as good as the results of routine bacteriological examination. For instance, in a series of 83 tuberculous effusions notified in this area during 1953–58, bacteriological proof was obtained in 28 only—i.e., 33·7%. Investigations included in practically every case culture and guineapig inoculation of pleural fluid, sputum culture, or gastric lavage. The present practice of prolonged chemotherapy, with or without corticosteroids, in cases of pleural effusion makes a definite diagnosis essential, and pleural biopsy should form part of the initial examination of all such cases.

In malignant effusions, pleural biopsy has often supplied a definite diagnosis, and this was particularly so in cases connected with peripheral bronchial carcinoma. In 6 such cases, where all the usual methods of investigation were negative, including bronchoscopy, bronchograms, and examination of sputum for malignant cells, 4 were diagnosed by means of pleural biopsy (oat-cell carcinoma in 2 and squamous-cell in the others). In 1 of the latter, malignant cells were actually seen within the lumen of a lymphatic vessel.

1. Baker, J. P., Farley, J. D. *Brit. med. J.* 1958, ii, 1390.

Another condition frequently seen in clinical practice is pleural effusion following at varying intervals mastectomy for carcinoma of the breast. Of 4 such cases, biopsy was positive 3 times, and in 2 of these a fairly confident opinion was given on the mammary origin of the tumour.

Technically the method is simple, and we have used the Harefield needle as described by Abrams [1] with remarkably few difficulties. There was no bleeding in any case, and a small pneumothorax was produced in 3 cases only. 4 specimens, or 1 in 10, were inadequate, consisting of intercostal muscle only, or of shreds of pleura insufficient for histological examination. In 1 other case, though the specimen was inadequate, a confident diagnosis was made from clumps of malignant cells attached to minute strands of pleura.

We have not found the method of great help in effusions seen in cases of rheumatoid arthritis or in obscure collagen conditions. Also, in my experience, pleural biopsy does not afford a definite diagnosis in acute inflammatory conditions, where the histological picture is frequently non-specific.

I am indebted to Dr. F. Hampson, area pathologist, for the histological reports.

Central Chest Clinic,
Battle Hospital,
Reading.

A. J. KARLISH.

TREATMENT OF BREAST CANCER

SIR,—Professor McWhirter [2] ended with a plea for an agreed system of clinical staging. Though essential, this may fail to show a difference in survival following simple and radical mastectomy if comparison is limited to five-year figures.

In an earlier publication [3] he defined the disputed group. They are those whose only metastases are axillary, and he estimated that this group amounted to only 14% of all sufferers from the disease. In the light of Saphir's and Amromin's work [4] this may be an underestimate, but it nevertheless serves to emphasise the relative smallness of the group. It would be by survival in these alone that a difference of effectiveness between radical and simple mastectomy could be displayed; yet it seems possible that a similar number of them survive either method by five years. This tends to invalidate comparison of five-year survival-rates. Indeed, it is worth noting that 22 of 100 Boston patients, though perhaps less afflicted at the outset, survived five years without any treatment at all.[5]

Edinburgh's position on the graph drawn earlier in your columns [6] was somewhat hypothetical. The graph sought to show, first, that five-year survival is related directly to the proportion of patients in the operable group with histologically confirmed axillary invasion and, second, that the Edinburgh treatment is at least the equal of the Mayo Clinic's. Essential to their position on the graph were the axillary invasion rates from Edinburgh and the Mayo Clinic, and, since the axilla is no longer removed there, Edinburgh's position depended on an estimate. This was derived from the period between 1935 and 1940 when radical mastectomies were done on as many as 72% of Edinburgh patients—only 221 being inoperable among a total of 790.[7 8] The estimate, therefore, unless I have misunderstood the headings above Professor McWhirter's tables, seems inapplicable to the 56% later "assigned to the operable category" [3]; for, presumably, axillary invasion would have befallen almost every one of those considered inoperable. Therefore the reduction over the years in the proportion considered to be operable represents a numerical movement of invaded axillæ from operable into inoperable categories. This would lower the estimate and, as a consequence on the graph, Edinburgh's position matching the Mayo Clinic.

Even so, re-study of 30 axillæ pronounced innocent after routine microscopy revealed metastases in 10,[4] and axillary invasion rates therefore provide no firm criterion of the amount of selection unless they are accompanied by statement of the number of nodes and sections examined.

Your leading article [9] put this question: "Since logic points to the futility of axillary dissection when no metastases exist there, what purpose can radical mastectomy serve?" I am sure you will agree, Sir, that any wisdom in that logic is only of hindsight, for routine microscopy finds axillary metastases in 40% of stage-I patients,[10] while extra sections may enlarge this figure to 60%.[4] The answer to your question is that radical mastectomy serves the purpose of removing these metastases. Further, there is no reason to suppose that it is less effective or safe than radiation. For example, within five years of Haagensen's 356 radical mastectomies only 4 patients developed axillary recurrence.[11] Cancer cells have been found in axillary nodes secondarily excised after gamma-radiation between the wars [12] and after modern X-radiation in Edinburgh,[13] but since these axillæ are not routinely excised the frequency of such persistence cannot be known.

Comparison of ten-year figures is of more interest. For those assigned to the operable group the Edinburgh ten-year figure is 39%.[3] The corresponding result, omitting decimal places, from Gordon-Taylor's and from Haagensen's radical mastectomies is 49%.[11 14] Each of these two surgeons avoided routine prophylactic radiation. Halliwell,[15] from figures admitted to be small (a total of 66 patients in 3 Steinthal stages), concluded that "it is clear that for no type of growth are the results as good where prophylactic X-ray treatment is carried out". Later Barling [16] saw that Gordon-Taylor's results would probably lead to a decline in routine prophylactic radiation. As criticism should not come o'er radiotherapy with its younger days it is of interest that in 1958 there came from the Holt Radium Institute a preliminary communication [17] reported to show that the results are "effectively identical whether the patients were treated by irradiation prophylactically or merely carefully followed up and only irradiated if necessary".

Further, there recently came from Birmingham [18] an analysis showing "a marked increase in the number of patients with distal metastases in the irradiated groups". This recalls Professor McWhirter's fear [3] that the hyperæmia induced by dosage sublethal to cancer cells may do harm by promoting the spread of those cells.

I will not now seek space for a full consideration of arm œdema and of the incidence of parasternal and supraclavicular deposits. It seems inescapable, however, that in the present state of knowledge it is preferable to remove with the breast the axillary mass of fat and lymphatics rather than to rely upon radiation of this area in stage I and, though the limits of this stage are still in process of being defined,[19 20] in early stage II also.

Launceston General Hospital,
Launceston, Tasmania.

W. W. WOODWARD.

1. Abrams, L. D. *Lancet*, 1958, i, 30.
2. McWhirter, R. *ibid.*, 1958, ii, 1060.
3. McWhirter, R. *Brit. J. Radiol.* 1955, **28**, 128.
4. Saphir, O., Amromin, G. D. *Cancer*, 1948, **1**, 238.
5. Daland, E. M. *Surg. Gynec. Obstet.* 1927, **44**, 264.
6. Bond, W. H., Waterhouse, J. A. H. *Lancet*, 1958, i, 430.
7. McWhirter, R. *Proc. R. Soc. Med.* 1948, **41**, 122 (tables VIII and X).
8. McWhirter, R. *in* British Surgical Practice, vol 2, p. 475 (tables IX and XI). London, 1948.
9. *Lancet*, 1958, i, 249.
10. Smithers, D. W., Rigby-Jones, P., Galton, D. A. G., Payne, P. M. *Brit. J. Radiol.* 1952, suppl. 4.
11. Haagensen, C. D. Diseases of the Breast. Philadelphia, 1956.
12. Paterson Ross, J. *Brit. J. Surg.* 1939, **27**, 231.
13. Ackerman, L. V. *Cancer*, 1955, **8**, 883.
14. Gordon-Taylor, G. *Ann. R. Coll. Surg. Engl.* 1948, **2**, 60.
15. Halliwell, A. C. *St. Thom. Hosp. Rep.* 1924, **48**, 213.
16. Barling, S. *Brit. med. J.* 1938, ii, 1278.
17. Paterson, R. Joint meeting of Liverpool Medical Institution and Manchester Medical Society. See *Brit. med. J.* 1958, i, 865.
18. Bond, W. H., Kunkler, P. B., Waterhouse, J. A. H. *ibid.* p. 643.
19. Handley, R. S. International Cancer Congress. See *Lancet*, 1958, ii, 139.
20. Haagensen, C. D. Carcinoma of the Breast. New York, 1958.

STAGING OF CANCER

SIR,—Dr. Frank Ellis's letter of Jan. 3 raises some important points concerning the proposed T.N.M. system for staging breast cancer. There is some truth in his contention that the proposed method may fall between two stools, and I agree that it may be better to use a carefully devised form. However, even a special form, prepared with the greatest care, may not ensure that clinicians record information in such a way that it can subsequently be used for accurate staging. For this reason there would be some merit in printing the list of T.N.M. definitions (as approved by the council of the Association of Surgeons and the council of the Faculty of Radiologists in November, 1957) alongside the relevant parts of a modest elaboration of the form at present issued by the Registrar General's Office. It would, of course, be possible further to elaborate certain parts of the T.N.M. system, such as group T_3, which is specifically mentioned by Dr. Ellis.

Dr. Ellis rightly reminds us that it is possible for the same case to be staged differently by different surgeons, but he is incorrect in saying that the surgeon who stages *least* strictly will get the best results. It is, in fact, the stricter stager who gets the better results; and this is brought out in the accompanying table which appeared

THE EFFECT OF DIFFERENT STANDARDS IN STAGING ON FIVE-YEAR SURVIVAL

(Staging of 1000 breast carcinoma cases by two observers. Hypothetical example of effects of a second observer, with stricter standards, transferring cases from Stage I to II, II to III, III to IV)

Observer A				Observer B			
Stage	No.	Surv.	%	Stage	No.	Surv.	%
I	300	195	65	I	240	163	68
II	300	105	35	II	300	123	41
III	300	30	10	III	300	42	14
IV	100	1	1	IV	160	3	2
	1000	331	33		1000	331	33

in the *Canadian Medical Association Journal*.[1] Though the figures given in this table are purely hypothetical, it is important that all should remember how much the survival-rate in different stages can be influenced by varying standards in clinical staging.

Radlett, Herts. REGINALD S. MURLEY.

BACTERIA AND BEDSCREENS

SIR,—In your annotation of Jan. 3 you state that the possibility of curtains harbouring bacteria-laden dust has not been seriously investigated.

In a hospital in this group a 14-bedded general surgical ward has, for the past twelve months, been set aside for an intensive investigation into some of the possible causes of wound sepsis. Among the factors considered were the curtains. These are made of cotton material and are of the "pull round" type. Sampling was carried out by means of "sweep plates",[2] the culture medium employed being nutrient agar containing phenolphthalein phosphate.[3] During 1958, sampling was carried out at weekly intervals, 250 separate investigations being made. *Staphylococcus pyogenes* was isolated from 134 (54%) of these samples.

On one occasion clean curtains which had been through the high-pressure steam steriliser were put up around the bed of a patient who had a staphylococcal wound infection of known phage type. In less than 24 hours the same phage type of staphylococcus was isolated in considerable numbers from the curtains.

These findings appear to bear out your contention that curtains may make a substantial contribution to aerial contamination.

Portsmouth. K. E. A. HUGHES.

1. Murley, R. S. *Canad. med. Ass. J.* 1956, **74**, 427.
2. Blowers, R., Wallace, K. R. *Lancet*, 1955, i, 1250.
3. Barber, M., Kuper, S. W. A. *J. Path. Bact.* 1951, **63**, 65.

WORLD SUPPLY OF UNSATURATED OILS

SIR,—Those actively engaged in the problem of dietary regulation of serum-lipids have become aware that the choice of unsaturated oils is not as unlimited as the grocer's shelves would lead us to suppose. As success with vegetable-oil-containing diets, prescribed currently only for small groups, is projected in our thinking upon a larger population, the problem of the supply of vegetable oil arises. In the United States corn (maize)-oil production is inadequate for any broad programme. In Britain, the Board of Trade import restrictions are blamed by Dr. Bourdillon [1] for depriving special groups of the benefits of corn oil. The limited world supply of corn oil is probably the real difficulty.

Most of the world's corn is grown in the Americas (see table) [2] and it is a relatively insignificant source of oil. In the United States corn oil contributed only 2·7% of all fats and oils produced for food in 1955–56.[3] If all corn processed in the United States in that year had been converted to corn oil, it would have provided only 7% of the year's supply of edible fats and oils. Corn oil is a secondary product and there is little possibility of a significant increase in supply. One bushel of corn yields only 0·8–1·5 lb. of oil (depending on the processing method) as compared with 11 lb. from a bushel of soybeans. Corn oil certainly cannot be a major source of unsaturated fatty acids.

If unsaturated oils are to be an integral part of the world's food the supply must be capable of further expansion. Half the world's supply of seed oils is grown in Asia, the rest in Europe, Africa, and the Americas (see table). Soybeans and cottonseed make up over

WORLD PRODUCTION OF MAIZE AND OIL SEEDS, 1956 (EXCLUSIVE OF U.S.S.R.)

—	World supply*	North and Central America† (%)	South America† (%)	Europe † (%)	Asia † (%)	Africa† (%)
Maize ..	163,900	57·6	7·6	10·9	17·2	6·7
Total oil seeds	64,900	33·0	5·1	2·8	51·0	8·1

—	World *	World supply (%)	North America † (%)	Latin America † (%)	Europe † (%)	Near East † (%)	Far East † (%)	Africa † (%)
Soy beans ..	24,000	37·0	51·7	—	—	—	47·8	—
Cottonseed	14,500	22·3	33·7	14·4	—	10·5	35·5	—
Ground nuts	13,100	20·2	5·6	5·0	—	—	63·5	23·7
Rapeseed ..	6,400	9·8	2·1	—	8·3	—	89·0	—
Linseed‡ ..	3,600	5·5	—	—	—	—	—	—
Sesame ..	1,750	2·7	—	—	—	17·0	—	72·0
Sunflower ..	1,650	2·5	—	43·5	42·5	6·7	—	—

These data are taken from Year Book of Food and Agricultural Statistics F.A.O., 1958.†

* World supply given in 1000 metric tons.
† Supply by continents as percentage of world supply.
‡ Not used for edible products.

half the Western world's oil-seed crop, the greater part of which is grown in the Americas. Both soybean oil and

1. Bourdillon, R. B. *Lancet*, 1958, ii, 420.
2. Year Book of Food and Agricultural Statistics; XI, part 1, 1957. F.A.O. Rome, 1958.
3. The Fats and Oil Situation (FOS, 181) Nov. 26, 1956, U.S. Department of Agriculture, A.M.S.

cottonseed oil are produced cheaply, but soybean oil has the greater potential to meet future demands. The soybean-oil industrial consumption in the United States doubled from 1950 to 1956 (from $1^1/_2$ to 3 billion lb.) while cottonseed oil remained the same (1·3 billion lb.) during the same period.

It is suggested that in experimental diets proposed to reduce plasma-lipids, preference be given to soybean oil, if it is proven as effective as the others, because of its relatively abundant supply.

Research Division, Cleveland Clinic, Cleveland, Ohio.

HELEN B. BROWN
IRVINE H. PAGE.

CANCER: TELLING THE PUBLIC

SIR,—The public as a whole remain appallingly ignorant about cancer [1]—its early symptoms, course, and possible treatment. Usually months, rather than days, elapse before the patient consults a doctor. Often a woman with a lump in the breast or abnormal losses of blood does not attach enough importance to them; but more often she does not want her fears confirmed. She may not even know that cancer starts as a local condition and is often curable. Is it fair then for the surgeon to say "If only you had come to me earlier, I could have cured you"—when she has never been told, or never brought to understand, the advantage of prompt investigation?

I agree with Mr. Malcolm Donaldson [2] that the reasons why cancer patients do not go to the doctor are fear and ignorance, and that the proper remedy for both is instruction. It is often said that such instruction induces more fear—that as a result of cancer propaganda the public develops cancer phobia. But Prof. Ian Aird [3] finds that the attitude of the American public has altered for the better since the myth of incurability has been exploded so far as the early case is concerned, and he has come over to the ranks of those who believe that the laity ought to be taught the fundamentals of cancer recognition in its early phase, long before the dreaded pain appears.

Three ways of reaching the public need further attention:

1. *Broadcasting and television.*—This is the easiest approach to large audiences, and in the right hands it can be successful. It requires great care, and very close liaison between surgeon and producer.

2. *Books.*—So many unsuccessful books have been written about cancer, by all sorts of people, from the orthodox to the highly unorthodox, that publishers are fighting shy of printing any more. Having written one called *Early Cancer for the Layman*, I could not find a single publisher who would look at it; but I have now had it rewritten by a laywoman, and shall start the round again.

3. *Lectures and discussions.*—Mr. Donaldson is to be warmly congratulated on the contribution he is making personally by addressing meetings and answering questions.

My idea would be to hold literally thousands of discussions (single ones and courses) conducted by general practitioners; for it is he who first sees the case and often looks after patients in their terminal stages.

A hotel room accommodating 20–30 people would be ideal. A chairman is installed and the doctor addresses the meeting for an hour. Coffee and biscuits are served, during which time a piece of paper is circulated for signing by those present. The chairman asks each one if he or she has any questions to ask. (In this way the shy ones are given an opportunity to take part.) Since people do not appreciate getting something for nothing, a silver collection concludes the debate. The local press might be invited.

For promoting and arranging lecture-discussions on this large scale, some central organisation would be needed; but in each region the help of medical schools would be invaluable. Has not the time come when such work as Mr. Donaldson has been doing individually should be reproduced on a national scale?

London, S.W.16. A. P. BERTWISTLE.

ANÆMIA IN PREGNANCY

SIR,—With great interest we read your editorial on this important subject, in which you emphasised the frequency of megaloblastic anæmia as a complication of pregnancy. You consider folic acid to be the only effective remedy in this condition. Vitamin B_{12} and intramuscular liver preparations are said to be of no avail in megaloblastic anæmia of pregnancy and the puerperium of temperate zones. We should like to make some comments on this statement, which suggests that megaloblastic anæmia of pregnancy is a single entity.

When crystalline vitamin B_{12} became available about ten years ago, a number of cases treated without success were reported.[1–4] Since then it has apparently been assumed that vitamin B_{12} is always ineffective in this condition, which should of course be distinguished from megaloblastic anæmia due to other causes such as addisonian pernicious anæmia or sprue occurring during pregnancy. This has led to the practice of treating these patients primarily with folic acid. Large doses of folic acid such as are usually given (10–30 mg. per day) are active in all types of megaloblastic anæmia, even those due to vitamin-B_{12} deficiency. In this way it is therefore impossible to distinguish vitamin-B_{12}-deficient cases from those in which folic-acid metabolism is disturbed. When megaloblastic anæmia of pregnancy is treated systematically first with moderate doses of vitamin B_{12}, and only if this proves ineffective with folic acid, it appears that megaloblastic anæmia of pregnancy and puerperium is not a single entity. In 1952 a case-report in your columns [5] described a patient in whom vitamin B_{12} was fully effective. The gastric juice contained free hydrochloric acid after histamine, while chemical determinations of the fat content of the stools gave a normal result. The blood-folic-acid activity was normal. This case was therefore considered an example of true megaloblastic anæmia of pregnancy. Since then we have observed 4 more cases in which vitamin B_{12} was effective out of a total of 11 patients. Details of most of these cases were reported elsewhere.[6 7]

We have also presented data about the serum-vitamin-B_{12} level and the folic-acid activity of the blood for *Streptococcus fæcalis*, which confirmed the dual nature of this disorder.[8] In cases reacting to vitamin B_{12} the folic-acid activity of the blood was normal, while the vitamin-B_{12} level was low. The reverse was found in a case which proved refractory to vitamin B_{12}.

In Canada Lowenstein and coworkers [9] also observed a good response to vitamin B_{12} in a number of cases of megaloblastic anæmia of pregnancy and puerperium.

In our opinion, therefore, both the systematic treatment with pure vitamin-B_{12} preparations and the analysis of these cases with microbiological estimations has confirmed the view expressed in 1946 by Watson and Castle,[10] that in megaloblastic anæmia of pregnancy one may deal

1. See, for example, the survey of public opinion by Paterson and Aitken-Swan (*Lancet*, 1958, ii, 791).
2. Donaldson, M. *Lancet*, 1958, ii, 790.
3. Aird, I. *Brit. med. J.* 1958, i, 1417.

1. Bethell, F. H., Meyers, M. C., Neligh, R. B. *J. Lab. clin. Med.* 1948, **33**, 1477.
2. Day, L. A., Hall, B. E., Pease, G. L. *Proc. Mayo Clin.* 1949, **24**, 149.
3. Ungley, C. C., Thompson, R. B. *Brit. med. J.* 1950, i, 919.
4. Haenel, U. *Klin. Wschr.* 1950, **28**, 471.
5. Nieweg, H. O. *Lancet*, 1952, ii, 491.
6. Nieweg, H. O. Vitamine B_{12} en foliumzuur-deficientie. Academisch Proefschrift, Groningen, 1953. Uitgeverij Excelsior, 's-Gravenhage.
7. Van Buchem, F. S. P. *Minerva Med.* 1954, **45**, 1513.
8. Nieweg, H. O., Faber, J. G., De Vries, J. A., Stenfert Kroese, W. F. *J. Lab. clin. Med.* 1954, **44**, 118.
9. Lowenstein, L., Pick, C., Philpott, N. *Amer. J. Obstet. Gynec.* 1955, **70**, 1309.
10. Watson, J., Castle, W. B. *Amer. J. med. Sci.* 1946, **211**, 513.

either with a lack of extrinsic factor or with a deficiency of Wills' factor.

We should like to add a more recent comment of Castle on this subject: " Few modern observers appreciate that the megaloblastic anæmia of pregnancy may be due to different deficiencies. These include folic acid, perhaps sometimes combined with ascorbic-acid deficiency, and less commonly vitamin-B_{12} deficiency as well.[11]

It is well known that administration of folic acid to B_{12}-deficient subjects may accelerate the development of nervous-system lesions. While we are not aware of reports of nervous-system damage in this condition, one should keep in mind the potential danger of systematic treatment with massive doses of folic acid. In our opinion the existence of vitamin-B_{12} deficiency should be excluded before folic acid is given. This may be done by a determination of the vitamin-B_{12} content of the serum. The *Lactobacillus leichmannii* method is sufficiently rapid for clinical use. If this method is not available, a therapeutic trial with vitamin B_{12} can be made. Daily reticulocyte-counts or, more rapidly, the response of the serum-iron concentration twenty-four hours or forty-eight hours after the administration of vitamin B_{12} may give a clue to the nature of the deficiency. We feel that in this way little time is lost in instituting adequate treatment in this serious condition.

Department of Medicine, University of Groningen, The Netherlands. F. S. P. VAN BUCHEM
H. O. NIEWEG.

EFFECT OF TUBERCULOSIS ON SEROTONIN-INDUCED BRONCHIAL SPASM IN GUINEAPIGS

SIR,—Bretey and Laroche [12] found that inoculation of guineapigs with *Mycobacterium tuberculosis* strongly increased their resistance to the bronchial spasm caused by histamine spray. At the same time tuberculosis does not protect guineapigs from bronchial spasm caused by acetylcholine spray. As serotonin inhalation gives rise to bronchial spasm very similar to that induced by histamine,[13] we investigated the effect of tuberculosis on the bronchial spasm of guineapigs caused by inhalation of serotonin.

The experiments were carried out on 20 female guineapigs. After application of a standard 0·3% serotonin spray, the length of time was measured until a sublethal bronchial spasm developed. The compound applied was serotonin creatinine sulphate (Sandoz S.A.)

The animals were then inoculated intraperitoneally with 0·1 ml. of a culture of *Mycobacterium tuberculosis* H37Rv grown in Dubos medium for six days. Thereafter the length of time until sublethal bronchial spasm developed was determined again at different intervals after the infection.

Weeks after inoculation	0	2	5	7
Minutes to development of sublethal bronchial spasm (average in 20 animals)	1·9	2·5	15	>15

These figures indicate that the guineapigs' sensitivity changes significantly after infection with *Myco. tuberculosis* and that the animals tolerate the serotonin inhalation for a long time without bronchial spasm. Thus, tuberculous infection of guineapigs modifies their reactivity not only to histamine but also to serotonin. The pathophysiological basis of this alteration needs further investigation.

National Institute for Tuberculosis " Korányi ", Budapest, Hungary. I. FÖLDES
E. KOMLÓS
J. PÁLINKÁS.

11. Castle, W. B. Yearbook of Medicine; p. 280. Chicago, 1959.
12. Bretey, J., Laroche, M. J. *C.R. Soc. Biol., Paris*, 1954, **148**, 244.
13. Herxheimer, H. *J. Physiol.* 1955, **128**, 435.

ÆTIOLOGY OF LEUKÆMIA

SIR,—Your review [1] of some recent work relating to " mouse leukæmia " falls far short, we believe, of giving your readers a fair presentation of the relevant facts. An uncritical premature acceptance of a seemingly plausible theory is a serious hindrance to progress in any field of research. We present the following points in the hope that they will permit your readers to make a more realistic appraisal of the status regarding the relationship of leukæmias of mice to the various agents and conditions considered in your leader.

The C3H strain comprises many substrains, one of which, C3Hf/Fg, has an incidence of nearly 80% neoplasms of the hæmatopoietic and lymphoid tissues. Substrains of N.C.I. origin have an incidence of such neoplasms of 10% or higher. The specific subline used by Gross, C3Hf/Bi, has, in our laboratories, an incidence of neoplasms of reticular tissues strikingly higher than 10% [2] and similar to that reported by Dulaney et al [3] and by Ida et al.[4] A 0·5% incidence is exceptionally low for any strain.

You discuss an incidence of 81% " leukæmia " reported by Gross to have been induced in C3H-strain mice by cell-free filtrates from leukæmic AK mice. In these particular experiments, Gross did not use cell-free materials (filtrates). In a later and summarising paper [5] he reports an incidence of 28% " leukæmia " in 328 C3H mice inoculated, as newborn, with cell-free filtrates.

You discuss the work of Friend, indicating that similar results were obtained in the induction of myelogenous leukæmia. It is clear to many workers in the United States that the lesion described by Friend does not fit into the morphological and biological patterns of granulocytic neoplasms, or any other type of neoplasm, recognised heretofore in mouse or in man. Friend did not describe the disease as myelogenous leukæmia in her publication to which you refer, but characterised it as " having the character of a leukæmia." In our opinion, this lesion would make a better laboratory prototype for the human disease, infectious mononucleosis, than it would for human leukæmias.

The work of Stewart and coworkers has been misinterpreted. You credit support to them for the hypothesis " that the leukæmogenic agents are viruses " and that " the leukæmic agents could be grown in tissue-culture . . ." Stewart and coworkers have not produced a significant increase in leukæmia, and the only relationship of these findings to leukæmia is the fact that the starting material was obtained from AK leukæmic mice.

Vertical transmission of pathogenic agents has been known for years, for example, in transmission of the mammary-tumour agent of mice, of certain rickettsial diseases, and in chicken lymphomatosis, and is not a phenomenon conceived or discovered by Gross. In contrast to your statement that " Gross has consolidated the evidence for the vertical transmission . . . of mouse leukæmia and certain mouse tumours . . .", Gross has in fact failed in the attempt to demonstrate infection of a strain of mice through more than one generation and the vertical transmission of " leukæmia virus ". In his latest paper reporting such efforts,[6] he stated, " An attempt to originate experimentally a leukemic C3H line has not succeeded, however."

Finally, may we point out that the term " leukæmia " as applied in the mouse, does not comprise a single neoplastic type. Biological and morphological characterisation of the many forms encountered in the mouse has been recorded by Dunn [7] and the trend observed by many workers to lump all

1. *Lancet*, 1958, ii, 30.
2. Law, L. W. 3rd Canadian Cancer Conference. New York, 1959.
3. Dulaney, A. D., Maxey, M., Schillig, M. G., Goss, M. F. *Cancer Res.* 1957, **17**, 809.
4. Ida, N., Kirschbaum, A., Taylor, H. G. *Proc. Amer. Ass. Cancer Res.* 1957, **2**, 217.
5. Gross, L. *N.Y. Acad. Sci.* 1957, **68**, 501.
6. Gross, L. *Acta hæmat.* 1955, **13**, 13.
7. Dunn, T. B. *J. Nat. Canc. Inst., Wash.* 1954, **14**, 1281.

such neoplasms into "mouse leukæmia" may indeed lead to false generalisations and conclusions.

We believe that information in this field is very valuable in our efforts to understand the genesis of cancer; but, if it is not to do more harm than good, this information must be painstakingly acquired, accurately reported, and judiciously reviewed.

H. B. ANDERVONT
CLYDE DAWE
THELMA B. DUNN
L. W. LAW
MICHAEL POTTER
M. F. STANTON.

National Cancer Institute,
Bethesda, Maryland, U.S.A.

PREPARATION OF HÆMOGLOBIN SOLUTIONS FOR ELECTROPHORETIC STUDY AND FŒTAL-HÆMOGLOBIN ASSAY

SIR,—To determine hæmoglobin type by paper electrophoresis, or fœtal hæmoglobin by the alkaline denaturation method, a relatively pure hæmoglobin solution, free of lipids, lipoproteins, and other blood-proteins, must be prepared from red blood-cells. The treatment of red cells by the method described below produces hæmoglobin solutions of 10–15 g. per 100 ml. The solutions are of such a stability as to allow shipment without refrigeration as well as storage at temperatures below 0°C for indefinite periods without denaturation as far as electrophoretic characteristics are concerned. This is in contrast to the instability of the usual aqueous hæmoglobin solutions. Our hæmoglobin solutions have been shipped to Australia and other distant points without denaturation. They have been opened and used repeatedly without becoming contaminated by bacteria or mould growth and have been stored at temperatures below 0°C, and warmed and recooled repeatedly without denaturation. 50% glycerol remains liquid at the usual temperatures of deep-freeze refrigerators.

Method

(1) Red blood-cells from 8–10 ml. of blood are washed three times with isotonic saline solution.

(2) The washed cells are hæmolysed. This may be done in one of several ways: freezing and thawing; the addition of a few mg. of saponin; or the addition of a drop of 'Triton X-100' wetting agent.* Contents of the tube are mixed to insure complete hæmolysis.

(3) A volume of chloroform estimated to be about half the volume of hæmolysed red cells is added, the tube is stoppered with a cork, and the mixture is shaken vigorously for one minute.

(4) The tube is centrifuged for five minutes at 2000 r.p.m. After centrifugation the hæmoglobin solution is decanted into a second tube.

(5) An equal volume of glycerol is added to the hæmoglobin solution and the contents of the tube are mixed. This material is satisfactory for shipping or storage. It may be used for the measurement of fœtal hæmoglobin by means of the alkali-denaturation technique. When the hæmoglobin is to be used for electrophoresis a portion of this solution is diluted with a solution of equal parts of glycerol and water to bring the hæmoglobin concentration to approximately 5%. When hæmoglobin solutions are to be shipped the solution should be allowed to remain in the concentrated form. Fœtal hæmoglobin estimations should not be run on solutions with a hæmoglobin concentration of less than 10%.

Department of Hematology,
Walter Reed Army Institute of Research,
Walter Reed Army Medical Center,
Washington, D.C.

DONALD N. HOUCHIN
RONALD W. ROBINETTE.

* Manufactured by Rohm & Haas Co., Washington Square, Philadelphia, Pennsylvania.

Obituary

DAVID HALLIDAY CROOM

B.A. Cantab., M.D. Edin., F.R.C.P.E.

Dr. D. Halliday Croom, who died on Jan. 7 at the age of 81, came of a well-known Edinburgh medical family and he spent his own life in running a single-handed family practice in the city.

He was the only son of Sir Halliday Croom, professor of midwifery and diseases of women in the University of Edinburgh. From Edinburgh Academy he went to Caius College, Cambridge. He took his B.A. in 1898 and returned to Edinburgh to study medicine, qualifying in 1903. After graduating he held house-appointments at the Edinburgh Royal Infirmary and the City Hospital and a clinical tutorship under the late Dr. George Gibson. He also spent some time abroad in post-graduate studies in Freiburg, Berlin, and Berne. He continued to keep in touch with hospital work through his appointment to the staff of Leith Hospital, but he had early chosen family practice as his specialty and he became an assistant to the late Dr. T. Burn Murdoch. After the 1914-18 war, during which he served with the R.A.M.C. in France, he settled in his own practice and quickly established himself.

R. W. J. writes:

"Dr. Croom had no panel patients and his only official appointments were those of chief medical officer to the Standard Life Assurance Company and of medical officer to Merchiston Castle School, but he won a large share of the affection and trust of his fellow citizens. Beneath his reserve they recognised his good sense and kindliness. His flair for diagnosis served his patients especially well in those days when the doctor had often to work without the comforting confirmation of laboratory tests. Fishing was his chosen recreation, perhaps because it chimed so well with his thoughtful and quiet disposition."

In 1908 Dr. Croom married a daughter of the late Dr. Blair Cunynghame. She survives him with a daughter and a son who is a physician at the Edinburgh Royal Infirmary.

SIDNEY RIDDIOUGH

M.A., M.B. Cantab., F.R.C.S.

Mr. Riddiough, honorary consulting surgeon to Addenbrooke's Hospital, Cambridge, died on Jan. 7 at the age of 67.

His father was J. T. Riddiough, of Bradford, and he was proud of having been to Bradford Grammar School which, he used to say, produced many doctors. He went to King's College, Cambridge, in 1910 and after obtaining honours in the natural sciences tripos and in the mathematical tripos he was for a time a master at The Leys School. He continued his studies at Guy's Hospital and he qualified in 1917. After serving as a captain in the R.A.M.C. he settled in general practice in Dewsbury. He was also surgeon to the Dewsbury General Infirmary, and in 1931 he took the F.R.C.S. About this time he moved to Cambridge, where he took over Dr. Charles Searle's practice. He only gave this up when he received consultant appointments. With his surgical and general practice he combined urology and venereology and, besides his appointment at Addenbrooke's, he was urologist to the Peterborough Memorial Hospital. He was a member of the county and borough councils and he also had many sporting interests.

C. W. A. S. writes:

"Mr. Riddiough, who was my friend for 28 years, since he took over my father's practice in Cambridge, was above all a man of many parts and talents. At one time he hunted regularly, latterly he shot and fished. He was an artist with a

May fly. He read widely in French, German, and Spanish and was most knowledgeable about music, of which he was very fond. To his medical knowledge and skill he added an unusual degree of common sense. A Yorkshireman, round of face, with a jovial countenance, he was the best of companions."

A. J. C. recalls early days in Cambridge:

"I met Sidney Riddiough first in 1915 in his room at The Leys School, where he sat affably receiving small boys bringing exercise books. Then two years later, when I was up for an exam, he was house-physician to Professor Bradbury at Addenbrooke's. Bradder seemed to relish mispronouncing his name—"This patient, Mister Rid-di-*owe*, has been smoking te-*back*-er" the old man would give out. Riddi*off* had a gift for mimicry and Bradder was his best impersonation. A small party of us that summer of 1917 hacked with Tibbs, and Riddiough always organised a race in some suitably large field. How those war half-dieted poor old screws flew as we came into the straight neck and neck. He fully maintained these sporting traditions, but we lost touch. And now he is no longer in the saddle or on the fens."

DOUGLAS HUTCHISON

M.B. Glasg., D.P.M.

Dr. Hutchison, who was killed in a climbing accident in Scotland on Jan. 3 at the age of 31, had spent the last three years as registrar and senior registrar in the department for children and parents at the Tavistock Clinic, London, and was in his final year of training at the Institute of Psychoanalysis.

He graduated M.B. from Glasgow University in 1950 and, after holding house-appointments, began his psychiatric training in Prof. Ferguson Rodger's department in 1953. After taking the D.P.M. he came to London in 1955 to train in child psychiatry and psychoanalysis.

He was an experienced climber and a former president of the Glasgow University Mountaineering Club. He had several difficult Alpine climbs to his credit. On his last climb he was a member of a party of six who set off in perfect weather to walk up the easy snow-covered north-west ridge of Ben More, Perthshire. He slipped without warning as he was crossing a frozen slope towards a sheltered corner on a lip of the corrie. He was unable to stop his slide with his ice-axe and fell 1500 feet.

Of his work at the Tavistock Clinic J. B. writes:

"There are too few young men of Douglas Hutchison's stamp coming into child psychiatry and his loss is correspondingly great. He was not afraid to learn from mistakes, while his modest charm earned him much affection. He read hard and thought for himself. Although reticent and slow to advance his own views, when he began to make contributions they bore the stamp of intelligent and careful thought. In his clinical work he never spared himself. It was this attitude of responsibility to his work that inspired confidence and, combined with high ability, led us to believe he would go far."

R. D. L., who was a fellow student at Glasgow, writes:

"After qualifying, Douglas Hutchison had first studied chemistry as an aspect of his lifelong pursuit of the truth, but he abandoned it and turned to psychiatry and psychoanalysis when he realised that the 'truth' he sought was that of his own existence and that of others. With truth, he loved freedom and this made it too difficult for him ever to suppose that the truth could be found ultimately in any particular theory. Thus his thinking had a rare untrammelled lack of bias. With humility, he combined exceptional talent: with a certain 'canniness' an unimpaired generosity. His customary reserve concealed a native wildness and did not cripple his capacity to rejoice."

ROBERT BERTRAM BLAIR

M.B. Edin., F.R.C.S.E.

Mr. Blair, who was for many years honorary surgeon to the Royal Infirmary and the Victoria Hospital for Sick Children in Hull, died on Dec. 31 at the age of 71.

He was born in Fife and studied medicine at the University of Edinburgh, graduating M.B. in 1911. After holding appointments at Edinburgh Royal Infirmary and the Radcliffe Infirmary, Oxford, he served as a volunteer in the R.A.M.C. As a surgeon specialist to the British Expeditionary Force, with the rank of major, he gave most of his attention to limb surgery.

After the war he settled in Hull and was appointed honorary assistant surgeon to the Royal Infirmary there in 1919. The following year he was appointed to the staff of the Victoria Children's Hospital, where he took special interest in orthopædic work. For 30 years he was also surgeon to the Hull Park Avenue crippled children's school. He was largely responsible for having a fracture clinic built at the Hull Royal Infirmary, and he took a leading part in the negotiations that led to the building of the Sutton annexe.

During the late war, besides his other work, he had E.M.S. beds under his care at Driffield, Beverley, and Cottingham. After his retirement in 1947 he continued to give valuable service by assisting in the casualty department at the Hull Royal Infirmary and in general practice. In 1945 he was elected a member of the board of management of Hull Royal Infirmary and chairman of the standing medical committee, and in 1948 he became a member of Hull "A" group hospital management committee. He also held an appointment as general surgeon with the committee.

E. M. D. writes:

"Mr. Blair was always one who bore his years lightly and seemed to be full of energy and a desire to continue in active medicine. He was a first-class surgeon and showed his special skill in orthopædics. He was particularly interested in treating orthopædic abnormalities in children, and many patients owe their subsequent activity to his kindliness and skill. He was always willing to advise his junior colleagues and to help assist them to develop their own knowledge and skill. When he was president of the Hull Literary and Philosophical Society, he conducted its affairs with dignity and indicated that his interests were spread over a much greater field than that of his professional sphere."

Mr. Blair leaves a widow, a daughter, and three sons, one of whom is a doctor.

Appointments

CUSACK, ANNYS M., M.B. Lond., D.P.H.: senior M.O., school health service, Leicester.

FOXEN, E. H. M., F.R.C.S., D.L.O.: consultant surgeon, E.N.T. department, French Hospital and Dispensary, London.

PLEYDELL, M. J., M.C., M.D. Lond.: M.O.H., Oxfordshire.

RUSSELL, J. D., M.B. Sydney, D.P.H.: assistant county M.O. and district M.O.H., Ryde, Sandown-Shanklin, and Ventnor, Isle of Wight.

South Western Regional Hospital Board:

JOHNSON, D. H., M.D. Brist.: consultant pathologist, Bristol clinical area.

KELLY, T. S-B., M.B. Manc., F.R.C.S.E., D.O.M.S.: consultant ophthalmic surgeon, Bath Eye Infirmary.

MONKS, P. J. W., M.B. Lond., F.R.C.S.: consultant surgeon, Exeter clinical area.

SIME, D. A., M.B. Edin.: S.H.M.O., Royal Western Counties Institution, Starcross, Devon.

Births, Marriages, and Deaths

BROWNE.—On Jan. 9, at Liverpool, James Charles Haines Browne, M.R.C.S., medical superintendent, Cunard White Star Line, aged 48.

PINES.—On Jan. 10, at his home, 38, Basing Hill, London, N.W.11, Noah Pines, M.B., aged 71.

Notes and News

WHITAKER'S ALMANACK 1959

MOST reference books are specialists, restricting their responsibility to offering detailed information about selected professions, institutions, or services. *Whitaker's Almanack* is more like a reliable and almost omniscient general practitioner. Each year it efficiently fulfils the promise of its front page and offers "an account of the Astronomical and other Phenomena and a vast amount of Information respecting the Government, Finances, Population, Commerce, and General Statistics of the various Nations of the World". The 1959 edition [1] has been stretched to include such relevant topics as satellites, Fuchs' crossing of the Antarctic, the new life peers and peeresses, the Homicide Act 1957, the New Towns of Great Britain, and the United Arab Republic.

University of London

The degree of M.D. has been conferred on the following:

P. B. Cook, Gordon Dutton, S. S. Epstein, D. A. F. McGill, Ariela Pomerance, Joan F. Zilva.

University of Bristol

At recent examinations for the degree of M.D. the following were successful:

P. C. Farrant, K. R. Gough, M. D. Turner.

University of Birmingham

The title of reader in experimental pathology has been conferred on Dr. K. W. Walton, senior lecturer in experimental pathology.

Dr. J. M. Bishop, at present lecturer in medicine, has been appointed to be senior lecturer and first assistant in medicine; Dr. P. C. Harris, at present lecturer in medicine, to be senior lecturer in medicine; and Dr. John Butler, at present university research fellow in the department of medicine, to be lecturer in medicine.

University of Glasgow

On Jan. 10 the following degrees were conferred:

M.D.—Mary C. Macdougall (with honours); J. M. Cameron, S. G. McAlpine, M. L. Paterson, J. S. Scott, C. McP. Smith (with commendation); A. T. McNeil, D. E. Munro, T. S. R. Train.

Ch.M.—F. C. Rodger (in absentia).

M.B., Ch.B.—John Adamson, E. F. Barron, W. A. S. Boyle, William Davidson, L. Kwamena Adasape Derban, Cecilie Donoghue, Evelyn M. Finnie, Patricia A. J. Freeman, A. B. C. Halliday, Alexander Harper, R. T. H. M. Harvey, J. G. B. Hendry, A. C. F. Kenmure, W. C. Kerr, J. D. McFarland, Donald McLaren, N. E. V. Marshall, W. M. Matheson, N. O. Mohammed, William Morris, Ian Morrison, J. M. Muir, Ulita A. Nair, J. A. Reilly, F. C. Robertson, E. T. Robinson, Lena C. Shaw, Gordon Somerville, William Thomson, D. F. Torley, J. D. Torrance.

Common Cold Research Unit

Up to the end of 1958 some 5921 volunteers had visited the unit. Nearly 700 have paid at least two visits, and many have been more than twice. The unit is appealing for more volunteers—men and women, between 18 and 45 and in normal health—so that the research team can continue their investigation without interruption during 1959.

At the Harvard Hospital, Salisbury, where the Common Cold Research Unit was established in 1946, comfortable living quarters are provided for the volunteers. Fares to and from Salisbury are paid up to a maximum of £3, and 3*s*. a day pocket-money is allowed to each volunteer. Further details may be had from the medical superintendent of the hospital.

Remuneration of Pharmacists

Hospital and health-centre pharmacists have been granted rises of pay as from Nov. 1, 1958 (P.H. circular no. 23).

The new salary ranges will be: for a full-time pharmacist in the basic grade, £605–£815; for a senior pharmacist £675–£865; for deputy chief pharmacists £700–£945 or £755–£1030, according to the category of hospital; and for chief pharmacists various ranges between £700–£945 and £935–£1335. The rates of payment of pharmaceutical students have also been increased.

1. London: Whitaker. Pp. 1188. 18*s*. 6*d*.

Royal College of Surgeons of England

At a meeting of the council on Jan. 8, with Sir James Paterson Ross, the president, in the chair, Sir Walter Mercer was appointed Robert Jones lecturer for 1959, Mr. H. R. Thompson Thomas Vicary lecturer for 1959, and Dr. H. J. Brennan Joseph Clover lecturer for 1960.

Dr. R. F. Woolmer, F.F.A. R.C.S., was appointed the first British Oxygen professor of anæsthesia.

A diploma of fellowship was granted to D. G. Kermode. The following diplomas were granted jointly with the Royal College of Physicians:

D.A.—Ronald Armstrong, D. W. Atherley, V. G. Balmer, Jeean Bheenick, Dhirendra Nath Biswas, Raymond Bliss, P. O. Bodley, T. A. Boliston, J. F. Bolt, R. H. Boyd, Anne H. Bristow, Sheila M. McN. Brownlie, Margaret E. Burns, George Canty, M. F. X. Carr, C. G. D. Clarke, H. L. Clarke, Pamela B. Clayton, Patricia A. Coates, A. F. Conchie, R. V. Consiglio, M. D. Cox, Martha K. Cuthbertson, H. J. Davies, J. A. H. Davies, M. W. L. Davis, Columba Devlin, H. R. Dingle, J. R. Donald, I. C. Dow, P. A. Eckstein, C. M. D. Edmonds, E. R. J. Emery, B. R. Eustace, Hilary K. J. Fisher, C. B. Floyd, S. B. Foulds, J. G. Francis, Abdul Ghani Gazi, Helen E. C. Gordon, M. A. Gormley, M. E. B. Hayes, V. B. Henry, J. C. Hill, Irene C. Hooks, Farkhanda Jabin Husain, John Hyland, Margaret James, A. M. C. Jennings, Anne F. Jones, Maria Jadwiga Kielbinska, T. D. Kimmet, D. W. G. King, D. H. King-Davies, P. J. W. Knell, Madhukar Gopalrao Kulkarni, A. G. Larson, Maire M. P. Leahy, P. F. S. Lee, D. S. Leede, W. J. Leishman, Yuin B. Ling, J. W. Lloyd, G. S. McCarthy, Nora M. McCarthy, T. N. McComb, J. G. McDonald, I. MacG. MacIntyre, J. C. McIntyre, G. K. McLellan, M. C. G. Mantell, A. R. Maude, Mary A. B. Murray, J. M. Nerney, F. A. Newton, A. D. G. Nicholas, T. M. O'Brien, M. J. Oldroyd, Peter Papworth, Shirley A. Peacock, Bruce Philpott, B. A. Poley, C. J. F. Potter, Satyavrat Ramrakha, V. E. Rees, L. A. Reitsma, D. S. Robbie, J. R. Samuel, Nirmal Sardana, Alan Shamash, Murigeppa Shidbasappa Sheshgiri, Murari Mohon Som, W. McA. Speirs, B. R. Stead, J. H. Stevens, R. V. Steward, Margaret M. Sutherland, W. E. Sweetapple, W. S. Sykes, Wasudeo Parashuram Thatte, M. A. Theeman, Helen L. Thompson, P. A. Tsoi-a-Sue, T. de L. Walker, J. R. W. Walsh, W. J. Walton, Audrey J. Wheeler, Valmae J. M. Wheeler, Doris S. Whiteford, Kathleen M. Whitfield, David Williams, R. V. Young.

D.P.H.—S. L. Adesuyi, Lily Arratoon, L. H. Brearley, Piti Changtrakul, Esfandiar Darabian, Jatindra Mohan Deka, Lilian Kerr, Christine Kirby, W. G. Lewis, Khan Muhammad Afzal Malazie, Esther E. Simpson, M. F. X. Slattery, D. J. Stephen, G. C. Young.

D.L.O.—Syed Yousuf Ali, Nikhilprokash Biswas, Deoram Khandoo Chaudhari, Damasio Vinicio Gomes Da Costa, Hrishikesh Das, Dallas Finney, Syed Ishrat Husain, Ali Afzal Khan, B. V. Lee, I. N. Lee, R. S. McKim, J. M. McLaughlin, Rashid Ahmad Mallal, T. A. Mulligan, Natwarlal Gangjibhai Patel, Pe Than Maung, Appaji Ramachandra Reddy, G. A. W. Sharrard, O. L. Thomas, G. Anwar Toma, Vaithialingam Vijayasegaram.

D.M.R.T.—Prabhat Banerjee, Kim Boon Chia, W. C. Constable, J. K. Donovan, Maureen B. Duthie, H. D. Friedberg, A. H. Laing, Maryam Khatoon Mallick, A. H. W. Nias, Rene Robillard, Mauricio Garcia Sainz, Akulananda Sarangi, Atar Deo Singh, Ngai-Chen Woo, Chun-Ming Yeung.

D.M.R.D.—K. R. Aberdour, J. E. B. Aling, Arnold Appleby, E. M. Bateson, Eleanor M. R. Besterman, G. P. Bradfield, Susan M. Broadbent, F. J. Brunton, E. H. Burrows, E. B. Davies, Ignatius Gunam Emmanuel, Frank Fletcher, L. V. Gould, Niranjan Gupta, P. M. Hacking, Alan Haylock, Mary A. Hewett, E. A. W. Houghton, V. H. Hutchinson, Minocher Nusserwan Jilla, Louis Kreel, Richard Leigh, L. R. Levin, J. J. McCavana, J. S. MacLean, D. J. Manton, Madhusudanlal Maskey, Adolph Meyer, T. J. O'Beirne, W. A. O'Brien, H. F. W. Pribram, Sira Srinivas Rao, C. J. Rhodes, R. E. Richardson, H. G. Row, John Roylance, J. J. H. Rymer, Surjit Singh Sandhoo, E. G. Shulman, Fritz Starer, H. B. Stentiford, Franciszek Czeslaw Trembalowicz, Jwala Prasad Udawat, Brenda D. Van Leuven.

D.P.M.—J. P. Baker, G. J. Barry, Isaac Berman, Ann D. Black, Stanford Bourne, Joyce E. Brest, M. W. Browne, Elizabeth M. Bruce, M. W. P. Carney, M. D. Cashman, A. D. Charles, S. I. Cohen, Carice Ellison, M. D. Enoch, N. D. Farnan, A. R. Foster, H. C. Fowlie, H. L. Freeman, Abraham Galea, Mabel L. Haigh, J. V. Halpenny, M. A. Hargreaves, R. W. Johnston, William Johnston, G. E. Langley, John McDonald, John Macintyre, Dorothy M. McWhirter, P. J. Mannion, D. H. Neale, J. W. G. Nixon, B. M. N. Pitt, Geoffrey Pollitt, Vahe Roupen Puzantian, W. H. Reid, Rodolfo Rodriguez-Arganaras, Daniel Rooney, L. F. W. Rowe, G. F. M. Russell, V. O. G. Smyth, D. I. Storey, Peter Sykes, James Warner, J. H. P. Willis, J. R. E. Wilson, Yip Chong Wong.

D.T.M. & H.—Kenchatte Kapaniah Appaji, Gajanan Gajre, D. H. Melville-Swarries, Hnin Yee.

D.Path.—Mirghani Yousif Ali, Bimal Chandra Bhattacharyya, H. N. Harrison, Thomas Manners, Tarakad Kasturi Narayanan, Don Simon Patabendi Sirilal Victor Jayawardena Wijesekera.

Medical Research Council

The Council invite applications for the following fellowships for 1959–60:

Fellowships in Clinical Research.—The Council are offering a further series of fellowships in clinical research, tenable at centres in the United Kingdom. These fellowships are open to suitably qualified medical graduates who wish to prepare for a career in clinical research. Stipend will be £950 per annum, rising to £1100.

French Government Exchange Scholarships.—Under the terms of a reciprocal arrangement with the Centre National de la Recherche Scientifique, two scholarships tenable at research institutions in France are offered to British workers in medical science. The scholarships will normally carry a maintenance allowance of 50,000–70,000 francs a month.

Forms of application for these fellowships may be had from the secretary of the Council, 38, Old Queen Street, London, S.W.1, with whom applications must be lodged by March 1, 1959 (March 31 for the French scholarship).

The Handicapped Child

The University of Liverpool department of studies in psychological medicine will hold a symposium on this subject at 76, Bedford Street South, Liverpool, 7, on Saturday, March 21. The speakers will include Dr. R. M. Todd and Dr. J. G. Howells. Further particulars may be had from Dr. H. Jarvie at the department, 77, Bedford Street South, Liverpool, 7.

Change of Name

The National Association for the Prevention of Tuberculosis is now to be known as the Chest and Heart Association. Tuberculosis will remain the Association's primary concern, but it will increasingly turn attention to prevention, research, and education in chronic bronchitis, lung-cancer, asthma, and diseases of the heart.

The London Clinic

Dr. Arthur Spence, director of pathology at the clinic, is retiring after five years there, and on Jan. 6 a reception was given in his honour.

Dr. Spence created a fully manned 24-hour-a-day service in the pathological laboratories of the clinic—an achievement which Lord Evans, in a short speech, described as "something which could not be equalled by any of the great hospitals in this country." He will be succeeded by Dr. Edward Hoare, who has been pathologist at the Edgware General Hospital.

Royal Society of Health

The health congress of this society will be held at Harrogate from April 27 to May 1, under the presidency of Lord Cohen of Birkenhead. Sir Ernest Rock Carling is to be president of a new section on radiation. A Chadwick lecture will be given by Dr. Gordon M. Fair, professor of public-health engineering, Harvard University, who will speak on new factors in man's management of his environment. Further particulars may be had from the secretary of the society, Mr. P. A. Wells, 90, Buckingham Palace Road, London, S.W.1.

Architect to the Ministry of Health

The Minister of Health and the Minister of Housing and Local Government have decided that in future their Ministries should have separate architectural establishments. At present, the architects working on behalf of the Ministry of Health are part of the staff of the Ministry of Housing and Local Government, and the chief architect of the Ministry of Housing and Local Government acts also for the Ministry of Health. Applications are being invited for a new post of chief architect in the Ministry of Health, carrying a salary of £3400 per annum.

The Ministry of Health's chief architect is to take charge of the staff engaged on the examination of the building schemes of local health authorities and of hospital boards. He will also be responsible for a unit which is studying the design of hospitals and other buildings connected with the health service, with a view to securing efficient and economical planning and construction. The unit has already published a study on operating-theatres.

Major-General T. F. M. Woods has been appointed honorary physician to the Queen in succession to Major-General F. J. O'Meara.

Prof. J. M. Yoffey has been appointed a knight of first class of the Order of the Danneborg in recognition of his services to the medical schools of the Universities of Copenhagen and Aarhus.

Dr. Harry Pigott has been reappointed a member of the National Assistance Board until Dec. 31, 1961.

Dr. Derek Wylie has left for a tour of the Middle East which is sponsored by the British Council.

A course for consultant dermatologists will be held at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, Lisle Street, London, W.C.2, from April 13 to 18. Applications should reach the dean by Feb. 20.

On Thursday, Jan. 22, at 8.15 P.M., at the Institut Français du Royaume-Uni, Queensberry Place, London, S.W.7, Dr. Bernard Halpern, director of research at the National Centre of Scientific Research, Paris, will speak on Allergie, Maladie d'Aujourd'hui, Fléau de Demain.

Diary of the Week

JAN. 18 TO 24

Monday, 19th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Lawson McDonald: Aspects of Atrial and Ventricular Septal Defects.

HUNTERIAN SOCIETY
8.30 P.M. (Mansion House, E.C.4.) Sir Russell Brain: Consciousness and Unconsciousness.

UNIVERSITY OF ST. ANDREWS
4 P.M. (Medical School, Dundee.) Prof. James Walker: Maternal-Fœtal Respiratory Exchange.

Tuesday, 20th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. W. S. Peart: Hypertension and the Kidney. (First of two Goulstonian lectures.)

UNIVERSITY OF LONDON
5.30 P.M. (London Hospital Medical College, E.1.) Prof. Paul Dell (Paris): Aspects of the Physiology and Pharmacology of the Brain Stem Reticular Formation.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. J. H. Dible: Pathology of Limb Ischæmia.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. G. L. M. McElligott: Non-Gonococcal Vaginal Discharge.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Prof. E. J. King: Infective Pneumoconiosis.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. E. J. Holborow: Pathology and Serology of Lupus Erythematosus.

SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Dr. John Price, Mr. F. W. Adams, Prof. C. A. Keele, Dr. E. R. Cullinan: The Problem of Drugs Not on the Poison List.

UNIVERSITY OF ST. ANDREWS
5 P.M. Prof. J. H. Burnett: Chemical Mutagenesis, Especially in Micro-Organism.

Wednesday, 21st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.15 P.M. *General Practice.* Dr. E. D. Forster, Mr. Aleck Bourne: Irregular Uterine Hæmorrhage.

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Wing-Commander J. K. Mason: Role of the Pathologist in Accident Reconstruction.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Fungi as Causative Agents of Human Disease.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. E. H. Hudson: Management of Pulmonary Tuberculosis in the Home.

OXFORD UNIVERSITY
5 P.M. (Radcliffe Infirmary.) Prof. H. L. Sheehan: Post-Partum Hypopituitarism. (Litchfield lecture.)

UNIVERSITY OF ST. ANDREWS
4 P.M. Dr. A. C. Turnbull: Uterine Function in Late Pregnancy or Labour.

Thursday, 22nd

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Professor Peart: Hypertension and the Kidney. (Last Goulstonian lecture.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. J. W. Dickson: Pathological Ossification in Nervous Disease with Special Reference to Traumatic Paraplegia. (Hunterian lecture.)

UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Dr. B. N. Halpern (Paris): Functions and Role of the Reticulo-Endothelial System in Immunological Processes.

UNIVERSITY COLLEGE, Gower Street, W.C.1
5 P.M. Prof. F. G. Young: Hormones and Metabolic Processes: (1) General Considerations. (First of three lectures.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. A. D. M. Greenfield: Regulation of the Blood Vessels in the Limbs.

INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
5.30 P.M. Professor Dell: Recent Advances in the Physiology of Wakefulness.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Prof. T. B. Fitzpatrick (Harvard): Biology of Melanin.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Dr. Winston Evans: Histogenesis of Ovarian Tumours.

UNIVERSITY OF ST. ANDREWS
5 P.M. Dr. Robert Leishman: Retinal Changes in Hypertension and Arteriosclerosis—their Diagnostic and Therapeutic Significance.

Friday, 23rd

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics and Gynæcology.* Mr. R. G. Law, Dr. Blair Hartley, Mr. R. C. Percival: Placentography.

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Prof. R. B. Welbourn: Surgical Treatment of Cushing's Syndrome and Adrenocortical Failure in Surgery.
4 P.M. Dr. Paul Beeson (Yale): Urinary Tract Infections.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. S. E. Birdsall: Chronic Ear Discharge.

The Ministry of Power has published its digest of statistics of pneumoconiosis in the mining and quarrying industries for 1957. Copies may be had from H.M. Stationery Office (3*s*.).

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